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Archives of Internal Medicine

VOLUME 47 FEBRUARY, 1931 NUMBER 2

BLOOD PRESSURE BEFORE AND AFTER OPERATION IN HYPERTHYROIDISM *

LEWIS M. HURXTHAL, M.D.

BOSTON

The relationship between blood pressure and hyperthyroidism is significant if some views of the present day are true. It is common knowledge that there is an increased pulse pressure in hyperthyroidism. Statements have been made that if this were continued over a sufficient time, cardiovascular changes and permanent arterial hypertension might ensue. Furthermore, it is the belief of some writers that the nontoxic adenomatous goiter can lead to similar changes over a period of years. There has been no adequate survey, as far as I am aware, to show that either active hyperthyroidism or prolonged but slight over-activity of the thyroid in otherwise clinically nontoxic goiter leads to permanent cardiovascular degeneration, hypertension or cardiac enlargement.

In observing patients who have been operated on for toxic goiter, one frequently finds the blood pressure higher after operation than before, although the basal metabolic rate is normal and the patient is clinically free from thyrotoxic signs or symptoms. One might assume that the preexisting state of hyperthyroidism had been a causative factor in the development of the vascular hypertension. These observations have probably led others to assume, and in certain instances have led me to wonder, whether or not there is any relationship. This study, therefore, was undertaken to determine: (1) the blood pressure before and after subtotal thyroidectomy; (2) the relationship between the metabolic rate, the type of goiter and the blood pressure; (3) a comparison between the blood pressure of patients with toxic goiter after operation and the blood pressure of nongoitrous persons.

MATERIAL USED

The ideal method of study in a problem of this kind is an analysis of a large group of consecutive cases. Complete follow-up data are difficult to obtain when patients are widely scattered over several states. While most of my patients return for examinations two or three times during the year following operation, less than one-fourth return regularly every three months during that time. I analyzed 458 cases of toxic goiter,

* Submitted for publication, July 7, 1930.

* From the Medical Department of the Lahey Clinic.

regardless of the type, the occurrence of postoperative myxedema or recurrent hyperthyroidism. I found, however, that selected cases had to be used for special purposes. This selection was made on the basis of completed data for the questions at hand. Only cases free from recurrent persistent hyperthyroidism or postoperative myxedema were included.

It seems hardly necessary to state that all cases diagnosed as hyperthyroidism were clinically thyrotoxic. Patients with hypertension and elevated basal metabolic rates who have no clinical evidence of thyroid toxicity are not considered as having hyperthyroidism, are not operated on and therefore are not included in this study.

OBSERVATIONS

Basal Metabolism Determination.—Unless the circumstances did not permit, the first basal metabolic rate in these cases was determined on the morning following the patient's admission to the hospital. A second basal metabolic rate was determined about the sixth day afterward. Unless the patient was unusually toxic or had some other complication, no further observations of the basal metabolic rate were made before the operation. In case that it was necessary to perform the operation in two stages, only one metabolic rate was usually recorded before the second stage. Six days after operation was generally the time at which the postoperative metabolic test was made.

The patients were asked to return every three months during the first year and once a year thereafter for observation. It was insisted that they enter the hospital on the night before observation; nothing was given to them by mouth after 8:00 p. m. that night. Phenobarbital was occasionally prescribed for restlessness. In the morning the patients were taken in wheel chairs to the metabolism laboratory, and after a rest of ten or more minutes the test was made. Thus, the best possible circumstances were provided for the estimation of the basal metabolic rate.

Blood Pressures.—A reading of the blood pressure was made when the patients were first examined either at the clinic or at the hospital. Readings of the basal blood pressure were made by trained technicians at the time of each metabolism test. Thus, all the readings of the blood pressure were made under ideal circumstances and under conditions that could not be improved.

BASAL BLOOD PRESSURE

Determinations of the blood pressure made under basal conditions are lower than those taken at other times.[1] A comparison of the basal

1. Addis, T.: Blood Pressure and Pulse Rate Levels, Arch. Int. Med. **29**:539 (April) 1922.

and clinical blood pressures distributed by decades is shown in tables 1 and 2. In my experience a basal systolic pressure of 140 mm. of mercury is often found to be from 150 to 160 mm., under the usual clinical conditions. A basal systolic blood pressure of 150 mm. of mercury, is therefore, in most instances, indicative of hypertension.

TABLE 1.—*Comparison of Clinical and Basal Blood Pressure by Decades (116 Cases of Exophthalmic Goiter)*

Decade	Clinical Blood Pressure, Mm. Hg	Basal Blood Pressure, Mm. Hg	Difference in Systolic Pressure, Mm. Hg
20 to 29	150/73	130/64	20/9
30 to 39	146/73	131/69	15/4
40 to 49	164/76	152/73	12/3
50 to 59	166/76	159/73	7/3
Average for all groups	155/76	132/70	
Average difference			23/6

TABLE 2.—*Comparison of Clinical and Basal Blood Pressure by Decades in Cases of Nontoxic Goiter*

Decade	Clinical Blood Pressure, Mm. Hg	Basal Blood Pressure, Mm. Hg	Difference in Systolic Pressure, Mm. Hg
20 to 29	126/78	113/64	13/14
30 to 39	133/84	117/70	16/14
40 to 49	150/90	131/77	19/13
50 to 59	154/90	144/83	10/7
60 to 69	155/86	142/80	13/6

TABLE 3.—*Average Basal Blood Pressure Readings by Decades in Cases of Exophthalmic Goiter and Toxic Adenomatous Goiter Before Operation*

	Exophthalmic Goiter (225 Cases)		Toxic Adenomatous Goiter (78 Cases)	
Decade	Basal Blood Pressure, Mm. Hg	Number of Cases	Basal Blood Pressure, Mm. Hg	Number of Cases
20 to 29	128/62	50		
30 to 39	131/67	50	127/72	12
40 to 49	144/77	50	137/74	19
50 to 59	155/73	50	158/81	33
60 to 69	164/70	25	161/87	14
		225		78

AVERAGE BASAL BLOOD PRESSURE IN HYPERTHYROIDISM BEFORE OPERATION

In table 3 are shown the basal blood pressure readings in the series of 225 cases of exophthalmic goiter and 78 cases of adenomatous goiter with hyperthyroidism. The group of 225 cases of exophthalmic goiter consisted of the patients requiring one or two stage operations and were selected according to decades. The 78 cases of adenomatous

goiter requiring one or more operations could not be selected in this way, as there was not enough material. As can be seen, there is a definite average rise of both systolic and diastolic pressures with increasing age.

AVERAGE BLOOD PRESSURE CORRELATED WITH BASAL METABOLIC RATE

The relationship between the average blood pressure by decades and the basal metabolic rate is shown in chart 1. While the pulse pressure and rate are indicative of the basal metabolic rate as shown by Read[2]

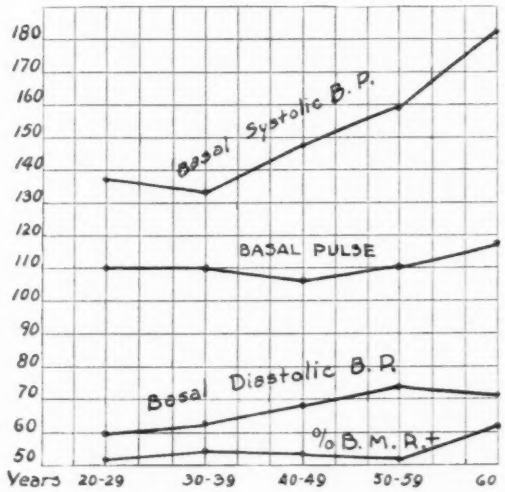

Chart 1.—Correlation of the blood pressure, the pulse and the metabolism in the different age groups of 100 cases of exophthalmic goiter (two-stage operation).

in cases uncomplicated by cardiovascular disease, my studies show that this relationship does not hold for the general run of cases.

EFFECT OF SUBTOTAL THYROIDECTOMY

The data on 50 cases of exophthalmic goiter that were observed for a year are shown in chart 2. These cases were selected because the patients had returned at regular intervals of three months and all the data had been recorded. The result at the end of three months in 100 cases of exophthalmic goiter in which two-stage operations were deemed advisable is shown in chart 3. Chart 4 records the events in 38 cases of adeno-

2. Read, J. M.: Basal Pulse Rate and Pulse Pressure Changes Accompanying Variations in the Basal Metabolic Rate, Arch. Int. Med. **34**:553 (Oct.) 1924.

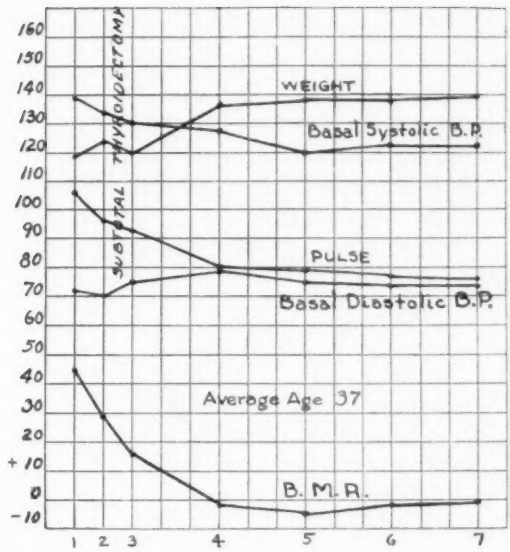

Chart 2.—Observations on fifty cases of exophthalmic goiter followed for one year: *1*, first observations; *2*, before operation; *3*, after operation; *4*, three months later; *5*, six months later; *6*, nine months later, and *7*, twelve months later.

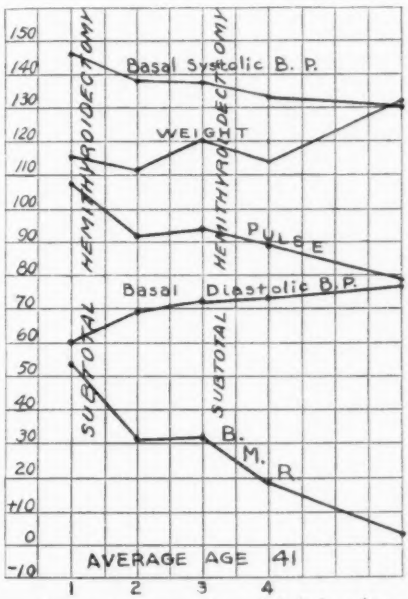

Chart 3.—Observations on 100 cases of exophthalmic goiter requiring two stage operations: *1*, first observations; *2*, after first operation; *3*, before second operation (six weeks later); *4*, after second operation, and *5*, three months later.

matous goiter with secondary hyperthyroidism. In these three groups, there were no cases in which there was persistent or recurrent hyperthyroidism or postoperative myxedema. The average age of the patients requiring one-stage operations was 37.7 years, whereas the average age of patients requiring two-stage operations was 41.7 years. The average age of the adenomatous group was 51 years. While the pulse pressure and the rate of metabolism averaged higher in the patients who required two operations, this relationship did not hold true for the patients with

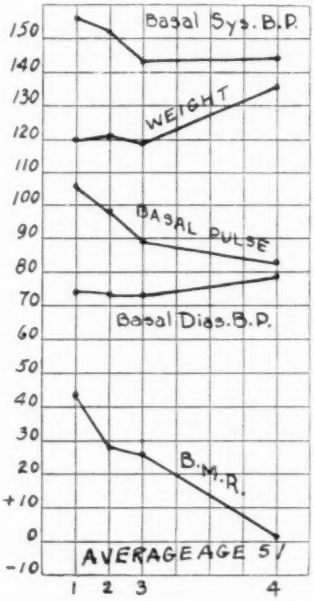

Chart 4.—Observations on thirty-eight cases of toxic adenomatous goiter (average age, 51): *1*, first observation before operation; *2*, second observation before operation; *3*, after operation, and *4*, three months later.

adenomatous goiter. It was noted that the blood pressure in the adenomatous group was higher than that in the group with severe exophthalmos, yet the metabolic rate was lower. The difference in blood pressure in the three groups was probably due to the greater frequency of hypertension with advancing years.

In table 4 are shown the average blood pressure readings in 458 cases of toxic goiter in which a subtotal thyroidectomy was performed in one stage. This includes all cases in which there was persistent or recurrent hyperthyroidism or postoperative myxedema. They were

divided according to the length of time during which they had been observed.

It may be noted from table 4, as well as from the preceding charts, that following operation there is a lower systolic pressure and a higher diastolic pressure. This also occurs before operation after a period of rest and the administration of compound solution of iodine. (All thyrotoxic patients in this study received compound solution of iodine, 10 minims [0.6 cc.] three times a day irrespective of the type of goiter). Of the cases requiring two operations, 46 per cent showed this change in blood pressure, i. e., a lower systolic pressure and higher diastolic pressure at the end of three months. However, 20 per cent showed an elevation of both the systolic and the diastolic basal blood pressures, while 14 per cent showed a reduction of both these blood pressures. The remainder had other minor variations. In the fifty cases of exophthalmic goiter

TABLE 4.—*Basal Blood Pressure Observations on 458 Consecutive Cases of Toxic Goiter (All Types)*

Number of Cases	Average Basal Blood Pressure	Basal Blood Pressure				
	Before Operation	After Operation	In 3 Months	In 6 Months	In 9 Months	In 12 Months
46	132/69	131/74	129/76	123/77	124/76	122/76
83	137/72	130/73	131/78	129/77	126/76	.....
136	137/72	132/73	129/74	126/73	.....	.....
193	138/69	131/71	129/81	.....	.....	.....
Total cases, 458						
Averages.....	137/70	131/70	129/77	126/77	125/76	122/76

which were followed with complete data for one year, 54 per cent showed a lower systolic and a higher diastolic pressure compared with that before operation; 26 per cent showed a lowering of both pressures, while 10 per cent showed an actual increase of both pressures. In thirty-eight cases of toxic adenomatous goiter, three months after operation, 40 per cent showed a lower systolic and a higher diastolic pressure, while 25 per cent showed both a lower systolic and a lower diastolic pressure; 21 per cent had a higher systolic and diastolic pressure after this interval.

In chart 5 is shown the effect of operation on the average basal blood pressures by decades in severe exophthalmic goiter (i. e., requiring two-stage operations), and in chart 6 is also shown the same effect in a group of 225 cases of all types of exophthalmic goiter selected to give reliable averages. The averages for the toxic adenomatous group before and after operation by decades are listed in tables 3 and 7.

One frequently sees patients with low or normal blood pressures who are toxic, emaciated, no longer markedly activated and even apathetic. These patients have a distinct rise in pressure when hyperthyroidism has been relieved. The explanation of this is difficult. The

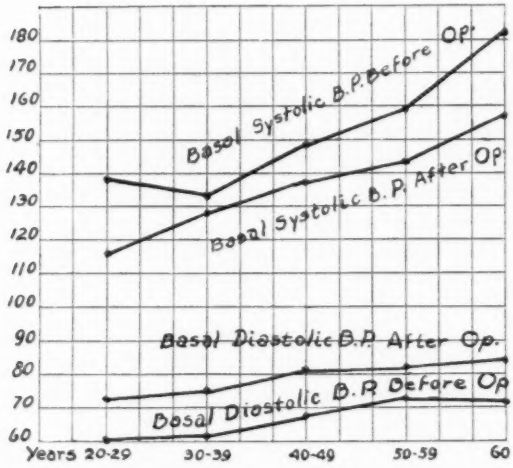

Chart 5.—The average basal blood pressure before and after two-stage operation in different age groups in 100 cases of exophthalmic goiter.

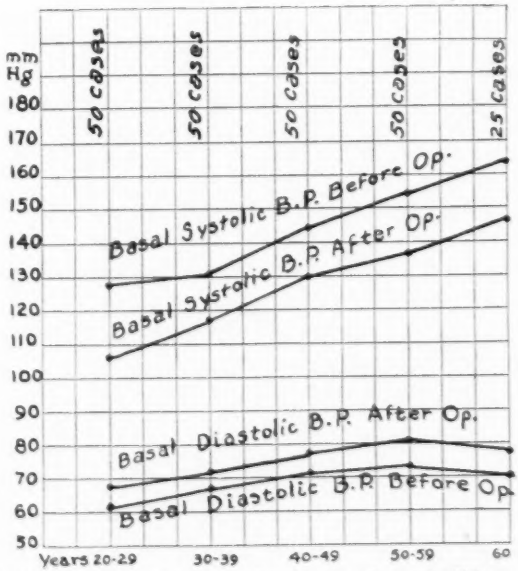

Chart 6.—The basal blood pressure by decades of age in 225 cases of exophthalmic goiter, before operation and from six to twelve months after operation.

observation that 20 per cent of the toxic patients had a rise in basal blood pressure following operation was surprising. Various factors may account for this: 1. A certain number had a prolonged rest in bed before coming to the hospital. 2. It is well known that a fall in blood pressure may take place when there is marked emaciation. 3. Some of these patients had an auricular fibrillation which returned to normal rhythm after the operation and permitted a more accurate determination of the blood pressure. I believe, however, that an auricular fibrillation may lower the blood pressure. Furthermore, the natural progression of an underlying hypertensive disease is a possibility.

The incidence of hypertension before and after operation in 458 cases of all kinds of toxic goiters is shown in table 5. An average basal blood pressure of 150 mm. of mercury or more was present in 26 per

TABLE 5.—*Analysis of Various Groups Before and After Operation in Relation to a Basal Systolic Blood Pressure of 150 Mm. Hg.*

Group	Per Cent Showing Systolic Blood Pressure of 150 Mm. Hg or More Before Operation		Per Cent Showing Rise to 150 Mm. Hg or Above After Operation	Average Age
	Before Operation	After Operation		
458 cases of all types: average of blood pressure before operation	26.8	13.7 (3 mo. to 1 yr.)	4.8	37.1
100 cases of severe exophthalmic goiter: initial blood pressure	42	23 (3 mo.)	11	41.2
50 cases of exophthalmic goiter: initial blood pressure	26	6 (1 yr.)	0	37.8
54 cases of adenomatous goiter with hyperthyroidism: initial blood pressure	62	44 (3 mo.)	7	51.2

cent of the cases before operation. From three months to a year following operation, 13.7 per cent still showed a basal pressure of 150 mm. of mercury or more; 4.8 per cent in which the average blood pressure was under 150 mm. of mercury before operation showed a final pressure higher than this figure. Thus, in this group of consecutive cases, approximately 18 per cent showed hypertension after operation. In the milder cases of exophthalmic goiter, 26 per cent showed an initial pressure of 150 mm. of mercury or more on the first examination, whereas only 6 per cent showed a blood pressure of this degree at the end of a year. On the other hand, in the severe cases of exophthalmic goiter in which the basal metabolic rate was normal at the end of three months, 40 per cent showed an initial basal pressure of 150 mm. of mercury or more before operation. At the end of three months, 23 per cent still had a basal systolic pressure of over 150 mm. of mercury, while 11 per cent showed a rise from below this figure to above it. In the adenomatous group, 62 per cent showed an initial pressure of 150 mm. of mercury

or more. After three months, 44 per cent still showed this pressure and 7 per cent showed a rise to 150 mm. of mercury or more. These data are also recorded in table 5.

The apparently higher percentage of hypertension in my cases of adenomatous goiter with hyperthyroidism may exist because of the greater age of the patients. Approximately 20 per cent of the patients with exophthalmic goiter were over 50 years of age, whereas 50 per cent of the cases of adenomatous goiter occurred after 50 years of age.

BLOOD PRESSURE AFTER OPERATION COMPARED WITH OTHER GROUPS

If one compares the average blood pressure readings of patients with toxic goiter after operation with those of other groups without goiter, the question of whether or not hyperthyroidism causes permanent vas-

TABLE 6.—*Comparison of Average Clinical Blood Pressure by Decades*

	Nongoitrous Patients		Nontoxic Goiter		1,000 Office Patients (Alvarez)		Diabetic Patients (Joslin)	
Decade	No. of Cases	Blood Pressure	No. of Cases	Blood Pressure	Blood Cases	Blood Pressure	No. of Cases	Blood Pressure
20 to 29	50	116/73	22	126/78	?	137*	50	111
30 to 39	50	120/77	61	133/84	?	130	50	124
40 to 49	50	137/81	52	150/90	Females Males	152 140	50	130
50 to 59	50	148/82	54	154/90	Females	165	50	155
60 to 69	50	164/93	20	155/86	Males	153	50	154
					(Age group 50 to 74)			

* Systolic.

cular hypertension should be at least partly answered. Table 6 shows the average clinical blood pressures by decades of 250 nongoitrous persons seen in the clinic. Tables given by Alvarez [3] and Joslin [4] are also shown. Joslin's patients comprised both men and women. Alvarez found that the blood pressure is approximately the same in men and women up to the age of 40; thereafter, a higher average was found for women. In my group of nongoitrous persons, 82 per cent were women, an incidence approximately the same as in the goitrous persons. In this table is also shown the average clinical blood pressures in goitrous patients who were considered nontoxic. The average blood pressures are somewhat higher than in the nongoitrous persons in our clinic, but they parallel rather closely those in the women studied by Alvarez.

3. Alvarez, W. C.; Wulzen, R.; Taylor, F. B., and Starkweather, E.: Blood Pressure in University Freshmen and Office Patients, Arch. Int. Med. **26**:381 (Oct.) 1920.

4. Joslin, E. C.: The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928, p. 712.

Table 7 shows the basal blood pressure in the same group of persons with nontoxic goiter as shown in table 2. Only with this group can comparisons be made with other groups, since the basal blood pressures are lower than those taken under the usual clinical conditions. In table 7 are placed for comparison the average basal blood pressures by decades in severe exophthalmic goiter, and in 225 cases of all grades of exophthalmic goiter, from 6 months to a year after operation (75 per cent were recorded at the end of a year). Thirty-eight cases of toxic adenomatous goiter before operation and at the end of three months are also included. It is to be noted (chart 7) that the averages of the 225 cases of exophthalmic goiter after operation parallel the averages of the cases of nontoxic goiter before operation. Thus, if the clinical blood pressures in the nontoxic cases parallel the clinical blood pressures of nongoitrous persons, there is no indication from this analysis that cure of

TABLE 7.—*Comparison of Basal Blood Pressure in Cases of Nontoxic Goiter Before Operation and in Cases of Toxic Goiter After Operation (by Decades of Ages)*

	Nontoxic Goiter Before Operation		Exophthalmic Goiter from 6 to 12 Mo. After Operation		Exophthalmic Goiter 3 Mo. After Operation (Severe)		Toxic Adenomatous Goiter 3 Mo. After Operation	
Decade	No. of Cases	Blood Pressure	No. of Cases	Blood Pressure	No. of Cases	Blood Pressure	No. of Cases	Blood Pressure
20 to 29	22	113/64	50	160/69	18	116/72		
30 to 39	61	117/40	50	118/72	23	128/75	8	124/69
40 to 49	52	131/77	50	130/77	26	137/81	11	129/76
50 to 59	54	144/82	50	137/81	27	143/82	19	153/83
60 to 69	20	141/80	25	147/77	4	158/83	9	156/88

exophthalmic goiter is followed by hypertension, at least not within from six months to a year later. The patients who required two operations show a higher residual average, but this is not a representative group. The presence of hypertension is often one of the reasons why an operation is done in two stages. The average basal postoperative blood pressures for the toxic adenomatous group are higher than those of the other groups in the fifth and sixth decades (chart 8). This is the only evidence pointing to the theory that hypertension may result from thyroid toxicity. It is doubtful if any conclusion can be based on 20 cases, and therefore this question is left open.

COURSE OF HYPERTENSION ASSOCIATED WITH HYPERTHYROIDISM

Chart 9 shows the course of fourteen patients with hypertension in whom basal and clinical blood pressure readings were obtained before operation and from six months to one year later. The patients were nontoxic clinically in spite of the fact that the average basal metabolic

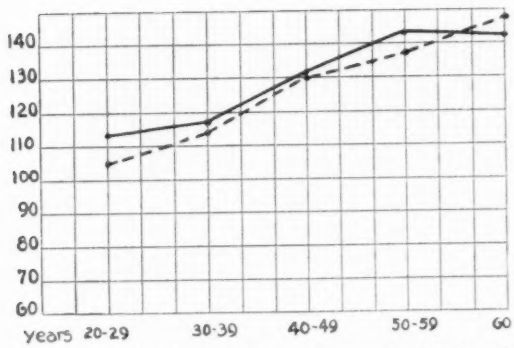

Chart 7.—The average basal systolic blood pressure by decades of ages in cases of nontoxic goiter (solid line) before operation, and in cases of exophthalmic goiter (dash line) from six to twelve months after operation.

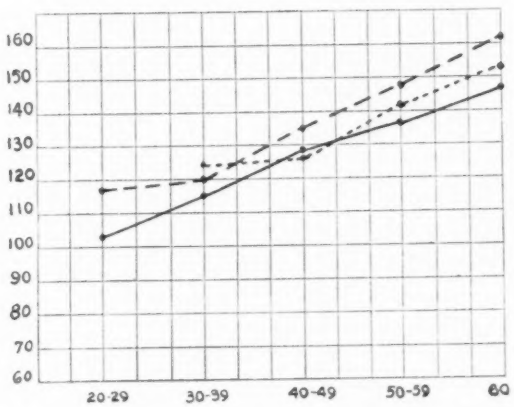

Chart 8.—Comparison of readings of blood pressure by decades of ages in cases of goiter after operation and in nongoitrous persons. The solid line indicates the exophthalmic group from six to twelve months after operation, the dash line office patients (nongoitrous) and the dotted line the toxic adenomatous group three months after operation.

rate was slightly higher than in the other cured cases. Thirty-eight other cases of hypertension were selected in which the data for either basal or clinical blood pressure were complete, but not for both. The averages were essentially the same as those already given. Aside from the slight drop in the basal systolic blood pressure and a slight rise in the diastolic pressure, hypertension is unchanged by thyroidectomy if the increased pulse pressure produced by hyperthyroidism is eliminated. The average age of this group of patients was 52.

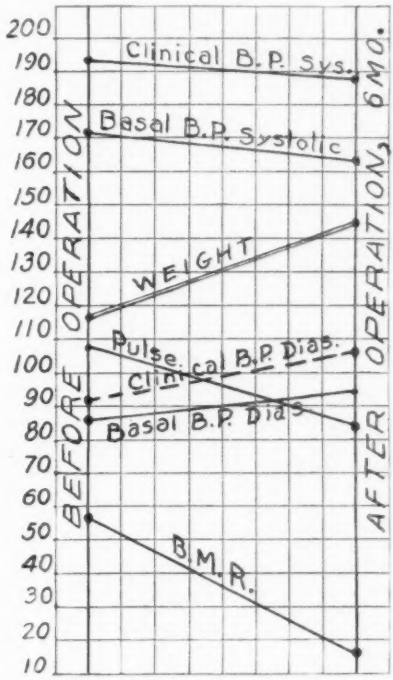

Chart 9.—Average blood pressure in fourteen cases of hypertension and hyperthyroidism before, and six months or more after, operation.

Another group of fourteen patients with toxic goiter who showed an auricular fibrillation before operation but a normal rhythm postoperatively and who were clinically free from thyrotoxic symptoms, was selected (chart 10). All these were considered hypertensive before operation. Only clinical blood pressures were recorded. The rise in both the systolic and the diastolic pressure was interesting and probably meant either that the blood pressure was lowered during the fibrillation of the auricles, or that the true pressure was not obtained. This may be

of some importance in individual cases, especially with congestive heart failure when associated with auricular fibrillation. An underlying hypertension may thus be overlooked.

OTHER OBSERVATIONS ON BLOOD PRESSURE

Mention should be made of the low or apparently absent diastolic pressure that is seen in extremely toxic cases. Pulsations may often be

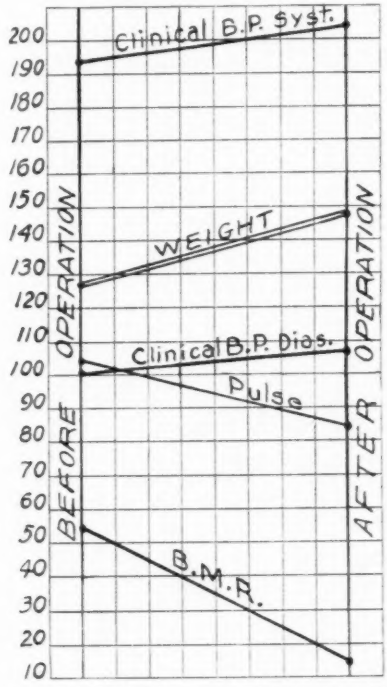

Chart 10.—Average clinical blood pressure in fourteen cases of toxic goiter with auricular fibrillation and hypertension before operation, and six months or more after operation when normal rhythm was present.

heard to the zero point. Whether or not this reading means an absent diastolic pressure is open to doubt. Occasionally, by simple adjustment of the stethoscope, a distinct change in sound may be heard in these cases between 30 and 60 mm. on the scale.

The characteristic snapping sounds heard in hyperthyroidism when the blood pressure is taken are of great value in diagnosis. This is particularly true with borderline cases. This characteristic sound is

rarely found in hypertension alone or in other conditions in which an increased pulse rate is present. If a choice between blood pressure readings and the auscultatory sounds had to be made as an auxiliary aid to the diagnosis of hyperthyroidism, I feel that the latter would be of greater value.

CONCLUSIONS

1. The blood pressure readings taken under basal conditions are lower than those otherwise taken. The difference is most marked in patients with hyperthyroidism.

2. The pulse pressure is increased in hyperthyroidism and decreased in about 50 per cent of the patients following relief from thyroid toxicity.

3. On the basis of averages there is no constant relationship between the height of the systolic blood pressure and the basal metabolism rate.

4. The average height of the blood pressure increases with advancing age.

5. The average basal blood pressure readings in cases of toxic goiter after operation and in cases of nontoxic goiter before operation run parallel.

6. The average basal blood pressure reading following relief from hyperthyroidism in exophthalmic goiter and from toxic adenomatous goiter is approximately the same in each age group up to 50 years, but thereafter it is slightly higher in the toxic adenomatous group.

7. The blood pressure in hypertension complicated by hyperthyroidism undergoes, on an average, the same change that patients with hyperthyroidism without hypertension undergo following operation.

8. In hypertensive patients with auricular fibrillation and hyperthyroidism, the average blood pressure is higher after operation when thyroid toxicity has been relieved and the normal rhythm has been restored.

9. There is no evidence in this study from which it can be concluded that hyperthyroidism leads to permanent cardiovascular hypertensive disease.

FUNCTION OF THE LIVER IN DIABETES MELLITUS*

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The intimate relationship of the liver to the pancreas, together with its association in carbohydrate metabolism, gives at least some justification for the assumption that hepatic dysfunction may be of frequent occurrence in diabetes mellitus. In an effort to corroborate or refute this supposition, the function of the liver in 100 persons with diabetes has been studied.

A review of the literature shows that numerous articles have been written concerning hepatic function and tests for the estimation of it, but only a few investigators have reported determinations in diabetic patients. Joslin [1] stated:

> The liver is assuming more and more the prominent rôle which it played in diabetes in the time of Claude Bernard. Its influence for good or evil, perhaps measured by the amount of glycogen which it stores, is more and more acknowledged. Perhaps the great "factor of safety" which the liver possesses because of its size hides its importance in the etiology of diabetes.

The coexistence of cholecystitis and diabetes has been considered frequently. Opie [2] showed by animal experimentation and clinical observation that there is a definite relationship between cholelithiasis and diseases of the pancreas. Lichty and Woods [3] endeavored to prove that cholecystitis was an etiologic factor in the production of diabetes. They reported 25 cases of diabetes and biliary tract disease in a series of 1,474 patients. Three of these apparently recovered from the diabetes after operations on the gallbladder. Adams [4] reviewed 6,500 cases of gallbladder disease and 1,101 cases of diabetes. Both diseases were

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1. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 175.

2. Opie, E. L.: The Relationship of Cholelithiasis to Disease of the Pancreas and Fat Necrosis, Am. J. M. Sc. **121**:27, 1901.

3. Lichty, J. A., and Woods, J. O.: The Significance of Glycosuria in Gall Bladder and Duct Disease, Am. J. M. Sc. **167**:1 (Jan.) 1924.

4. Adams, S. F.: Is Disease of the Gall Bladder a Cause of Diabetes Mellitus? Surg. Gynec. Obst. **41**:75 (July) 1925.

present in 131 patients, all of whom were over 40 years of age. Wilder [5] reported 20 cases of biliary tract disease in 58 diabetic patients examined post mortem. Sixteen of these had calculi.

Joslin [1] remarked:

> Gallstones are about 50 per cent more common among diabetics over 25 years of age than among a similar group in the community at large. Gallstones often precede diabetes and may precipitate it by direct extension of infection to the head of the pancreas. Diabetes is not only due to a disturbance of carbohydrate metabolism, but, as shown by Pflüger, Geelmüyden and Allen, an associated protein and fat disturbance.

In four Boston hospitals 211 necropsies were performed on diabetic patients over 25 years of age. Fifty of these, or 23.7 per cent, had gallstones. Bowen, Vaughan and Koenig [6] reported that from 1923 to 1928 at the Buffalo General Hospital 16 autopsies were performed on adult diabetic patients, and that of these 1 showed calculi and 3 cholecystitis. Surgeons are constantly observing at operation that all cases of chronic cholecystitis are associated with varying degrees of hepatitis and not infrequently with pancreatitis. Rabinowitch [7] said:

> There is much clinical and statistical evidence to prove that the association of diabetes and gallbladder disease is more than accidental, and that pancreatitis is generally recognized as a sequela of cholelithiasis and cholecystitis.

Jones, Castle, Mulholland and Bailey [8] investigated pancreatic and hepatic activity in sixty-eight cases of diabetes mellitus. They discovered diminished pancreatic activity in one half of the cases and abnormally high elimination of bile pigment in the duodenal contents in three fourths of the cases. They decided that undernutrition had an undesirable effect on both liver and pancreas, but that when this was controlled by efficient insulin therapy and diet there was a marked reduction in the pancreatic and hepatic abnormalities. Cholelithiasis occurred in 19 per cent of the cases. The average age of the patients was 51.

Rabinowitch [7] studied hepatic function in 130 cases of diabetes mellitus. He considered the phenoltetrachlorphthalein test insufficiently sensitive for the detection of early impairment of liver efficiency. In only 3 of 50 cases was the Wallace and Diamond method for estimations

5. Wilder, R. M.: Necropsy Findings in Diabetes, South. M. J. **19**:241, 1926.

6. Bowen, B. D.; Vaughan, S. L., and Koenig, E. C.: The Relation of Liver and Gall Bladder Disease to Diabetes, etc., Bull. Buffalo Gen. Hosp. **6**:41 (Dec.) 1928.

7. Rabinowitch, J. M.: The van den Bergh Reaction in Diabetes, Brit. J. Exper. Path. **7**:155, 1926.

8. Jones, C. M.; Castle, W. B.; Mulholland, H. B., and Bailey, Francis: Pancreatic and Hepatic Activity in Diabetes Mellitus: The Alterations, with Some Observations on the Etiology of the Disease, Arch. Int. Med. **35**:315 (March) 1925.

of urobilinogen in the urine found to give positive results. The indirect van den Bergh test was employed in all the cases. The results were not expressed in milligrams or units, but were referred to as positive when the colors were of greater intensity than normal. Thirty-four, or 26.1 per cent, had a positive van den Bergh reading, and the percentage of positive reactions was twice as great in the overweight subjects.

Diamond [9] performed the van den Bergh test in a large series of cases. In seventeen of these diabetes mellitus was present. Fourteen gave normal results. Three of the more severe cases in which no treatment had been given gave high readings for bilirubin: 1.1 units, 1.2 units and 1.4 units, or, expressed in milligrams per hundred cubic centimeters, 0.55, 0.6 and 0.7. He also found a high excretion of urobilinogen during acidosis and a return to normal with the administration of insulin. He concluded that despite the diversity of the functions of the liver a high value for blood bilirubin indicates a disturbance of the liver, unless due to hemolytic disease.

Bowen, Vaughan and Koenig [6] estimated hepatic function in twenty-three cases of diabetes mellitus. In none of their cases did the urobilinogen in the urine exceed 1:20, and only seven gave this reading. They evidently considered the finding of urobilinogen in this dilution indicative of hepatic dysfunction. The result of the quantitative van den Bergh test exceeded 0.6 units (0.3 mg.) in twelve cases, and 1 unit (0.5 mg.) in eight cases. Bromsulphalein retention was present in five patients, but the test was performed in only fourteen cases of diabetes. The lowest reading for blood sugar was 115 mg., the highest 548 mg. and the average 221 mg. They concluded that tests for hepatic dysfunction more regularly give positive results in cases of diabetes than in the group of alimentary glycosuria.

METHODS

The 100 diabetic persons were studied in the metabolic wards of the Philadelphia General Hospital. They were first examined and treated by the chief of the metabolic department and his associates. A history was taken of each patient, and a complete physical examination conducted, with all the usual or specially indicated laboratory tests. Later, studies of hepatic function were instituted. The urobilinogen, bromsulphalein retention, icterus index and direct and indirect van den Bergh tests were selected as the most satisfactory in the study of diabetic persons, and were used to obtain data concerning every member. All tests were conducted and blood specimens obtained early in the morning before the patients received breakfast. Studies of cholesterol were also done in the hope that some additional information would be obtained concerning cholesterol metabolism and its value in the prognosis of diabetes, as indicated by the 2,000 estimations reported by Rabinowitch.[10]

9. Diamond, J. S.: The Value of Routine Estimations of Blood Bilirubin, Am. J. M. Sc. **176**:321, 1928.

10. Rabinowitch, J. M.: Cholesterol Content of Blood Plasma in Diabetes Mellitus, Arch. Int. Med. **43**:372 (March) 1929.

The Wallace and Diamond[11] technic was used for estimations of urobilinogen. A series of accurate dilutions of urine was made, and only those readings were recorded that showed a definite pink color. Warm water was used in diluting the urine, and the final reading was made five minutes after adding the Ehrlich reagent. The specimens examined were usually portions of the preceding twenty-four hours' output. The urine was placed in covered mason jars containing toluol. They were kept in electrically operated refrigerators at 42 F. It was found that when urine is exposed to heat and light the value of the test decreases proportionately with the time elapsing after voiding. Samples examined soon after urination, or at different periods of the day, rarely furnished information greater than that obtained from properly cared for twenty-four hour specimens. A positive reaction in urine diluted more than twenty times was considered abnormal.

The bromsulphalein test as reported by Rosenthal and White[12] was found to be extremely satisfactory and without hazard of venous thrombosis or prolonged discomfort to the patient. A 5 per cent solution of 2 mg. of the dye per kilogram of body weight was slowly injected. A 5 cc. syringe was used and a twenty-four gage hypodermic needle, and when the injection was completed, about 5 cc. of blood was drawn into the syringe and reinjected, all of the dye being thus obtained and also the deposit of bromsulphalein about the wall of the vessel or adjacent tissues on withdrawal of the needle being prevented. A specimen was obtained exactly thirty minutes later, and any retention was considered indicative of hepatic dysfunction.

The icterus index was computed according to the Bernheim method,[13] modified by Murphy.[14] The test is easily performed, but unless extreme care is observed in collecting blood specimens and obtaining the serum subsequently, it is impossible to make accurate estimations. As a result of the large pigment content in the diabetic diet and the frequency of lipemia during the course of the disease, an accurate interpretation of the icterus index is often impossible. It was found more satisfactory to dilute the serum before reading with a phosphate buffer (p_H 7.4) than with physiologic solution of sodium chloride. In my opinion, the icterus index is a less reliable test in diabetic patients than the quantitative van den Bergh test.

The qualitative van den Bergh test was read at the time of adding the diazo reagent to the serum, as directed in the quantitative method of Thannhauser and Anderson.[15] The last procedure of their technic was modified by using cobalt standards in small test tubes and after centrifugation withdrawing the supernatant

11. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, with a Description of a Simple Quantitative Method for Its Estimation, Arch. Int. Med. **35**:698 (June) 1925.

12. Rosenthal, S. M., and White, E. C.: Clinical Application of the Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**:1112 (April 11) 1925.

13. Bernheim, A.: The Icterus Index (A Quantitative Estimation of Bilirubinemia); Aid in Diagnosis and Prognosis, J. A. M. A. **82**:291 (Jan. 26) 1924.

14. Murphy, W. P.: An Easy Method of Estimating the Amount of Jaundice by Means of the Blood Serum, Boston M. & S. J. **194**:297, 1926.

15. Thannhauser, J. R., and Anderson, E.: Methodik der quantitatativen Bilirubin Bestimmung in menschlichen Serum, Deutsches Arch. f. klin. Med. **137**:179, 1921.

fluid into similar test tubes and then reading rather than attempting a comparison in the centrifuge tubes.

Wallace and Diamond,[11] Eusterman,[16] Hall,[17] Piersol and Rothman,[18] Graham, Cole and Copher [19] and Foley [20] offer abundant data to indicate the value of these tests for the estimation of hepatic function and to aid in the interpretation of the results.

The normal results in the selected tests have been satisfactorily determined. All investigators agree that the retention of any bromsulphalein after thirty minutes should be considered abnormal and indicative of hepatic disease. Foley [20] examined 100 persons from the outpatient department of the Research and Educational Hospital. They were apparently free from gross pathologic changes of the liver. He stated, "Particular attention was taken to exclude cases in which a history of alcoholism or syphilis was obtained." Not one of these had any bromsulphalein retention after thirty minutes.

An icterus index reading of from 3 to 6 is accepted as the usual normal, and 99 per cent of Foley's [20] cases had 6 or less.

A positive reaction for urobilinogen in urine diluted twenty times is taken as the high normal. Piersol and Rothman [18] considered this the most delicate test for hepatic function and any elevation greater than 1:20 indicative either of hepatic injury or of excessive production of bilirubin.

The quantitative van den Bergh reaction is subject to greater variations in interpretation as to normal values. The average range is usually given as from 0.1 to 0.25 mg. or 0.3 mg. per hundred cubic centimeters. Van den Bergh,[21] McNee,[22] Hall,[23] Ravdin [24] Roberts,[25]

16. Eusterman, G. B.: Functional Tests of the Liver; a Clinical Review, Ann. Int. Med. **1**:53 (Aug.) 1927.

17. Hall, W. W.: The van den Bergh Reaction for Serum Bilirubin, with Notes on Interpretation and Technique, J. Lab. & Clin. Med. **12**:529, 1927.

18. Piersol, G. M., and Rothman, M. M.: The Practical Value of Liver Function Tests, J. A. M. A. **91**:1768 (Dec. 8) 1928.

19. Graham, E. A.; Cole, W. H.; Copher, G. H., and Moore, S.: Diseases of the Gall Bladder and Bile Ducts, Philadelphia, Lea & Febiger, 1928, pp. 337-398.

20. Foley, E. F.: Liver Function Tests, Arch. Int. Med. **45**:302 (Feb.) 1930.

21. van den Bergh, A. A. H.: Jaundice, Brit. M. J. **2**:498 (Sept.) 1924.

22. McNee, J. W.: Jaundice, Review of Recent Work, Quart. J. Med. **16**:390, 1923.

23. Hall, W. W.: Useful Hepatic Function Tests, U. S. Nav. M. Bull. **24**: 843, 1926.

24. Ravdin, E. G.: Clinical Value of the van den Bergh Test, Am. J. M. Sc. **169**:850, 1925.

25. Roberts, W. M.: Observations on the Nature of the van den Bergh Reaction, Brit. J. Exper. Path. **9**:107, 1928.

Andrews,[26] Anderson,[27] Rhamy[28] and Graham, Cole and Copher[19] agreed with these figures. Perkin,[29] after examining 50 presumably healthy persons, decided that from 0.05 to 0.35 mg. would include all normal cases. Diamond[9] gives from 0.2 to 0.4 mg. Schiff,[30] after examining 202 persons, concluded that a reading over 0.6 mg. is abnormal and said, "When higher values are quoted it is to care for cases of familial cholemia." Rowntree[31] and Greene, Snell and Walters[32] gave from 0.2 to 1 mg. and from 0.5 to 2 mg., respectively, as the normal range. In Foley's 100 clinical cases, 71 per cent showed less than 0.3 mg. and 95 per cent less than 0.5 mg.

Apparently there are sufficient data to conclude that from 0.25 to 0.3 mg. may be safely taken as the usual high normal.

EXPERIMENTAL DATA

After completing the investigations on the 100 diabetic patients, three main groups, A, B and C, were formed for study and comparison.

Group A.—The forty-eight members of group A afforded neither physical observations nor laboratory evidence indicative of dysfunction of the liver.

Group B.—The thirteen patients of group B could have been included in group A if nine (subgroup B-1) had not shown a very slight retention of bromsulphalein. This amount did not definitely measure 3 per cent and was recorded as from 0 to 3 per cent, thus indicating that the amount was too small to be estimated accurately and possibly would be ignored by some investigators or classified as a trace. The remaining four (subgroup B-2) showed only an elevated van den Bergh value. Two had 0.4 mg. and the others 0.5 mg. As this was the only indication of hepatic dysfunction, it is probable that the readings should not be considered abnormal in these cases.

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26. Andrews, C. H.: A Clinical Study of the van den Bergh Test in Jaundice, Quart. J. Med. **18**:19, 1924.

27. Anderson, J. H.: Examination of the Blood for Bile Pigment, Lancet **2**: 346, 1929.

28. Rhamy, B. W.: Estimation of Bilirubin in the Blood as an Index of Liver Function, J. Indiana M. A. **20**:212, 1927.

29. Perkin, F. S.: Blood Bilirubin, Estimation and Clinical Significance, Arch. Int. Med. **40**:195 (Aug.) 1927.

30. Schiff, Leon: Serum Bilirubin in Health and in Disease, Arch. Int. Med. **40**:800 (Dec.) 1927.

31. Rowntree, L. G.: Our Present Knowledge of Test of Liver Function, Proc. Inter-State Post-Grad. M. Assemb., North America, 1927, **3**:475, 1928.

32. Greene, C. H.; Snell, A. M., and Walters, Waltman: Diseases of the Liver: I. A Survey of Tests for Hepatic Function, Arch. Int. Med. **36**:248 (Aug.) 1925.

Group C.—From the thirty-nine patients in group C it was possible to obtain evidence indicative of hepatic dysfunction. At least one test in each case gave a positive result.

The special table with the individual laboratory data for group A is omitted, as the results of all the tests employed in the estimation of the hepatic function were interpreted as normal. With foci of infection in teeth, tonsils and sinuses excluded, all persons in group A were considered as having uncomplicated diabetes mellitus, except as follows: Patients 26 and 62 both had had cholecystectomies performed five years

TABLE 1.—*Data on Patients in Group B*

Patient	Sex	Age	Weight Lb.	Weight Kg.	Duration of Diabetes, Yr.	Units of Insulin Daily	Blood Dextrose, Mg.	Cholesterol, Mg.	Urobilinogen (Urine Dilution)	Icterus Index	Result, Qualitative van den Bergh Test	Mg. Bilirubin, Quantitative van den Bergh Test	Bromsulphalein Retention, %
Subgroup B-1													
17	F	45	309	140.1	2	140	145	170	None	4	Negative	0.2	0–3
31	M	71	192	87.1	0.5	13	155	140	1:20	6	Faint delay	0.3	0–3
36	M	50	132	59.9	1	25	120	220	1:10	4	Faint delay	0.3	0–3
37	M	51	155	70.3	12	20	97	250	1:20	6	Faint delay	0.3	0–3
40	F	55	137	62.1	1	54	102	135	1:1	6	Negative	0.3	0–3
80	M	57	113	51.3	5	5	97	240	1:20	6	Negative	0.3	0–3
81	F	68	152	68.9	6	9	93	235	1:20	4	Negative	0.2	0–3
45	F	42	123	55.8	1	69	130	175	1:1	4	Negative	0.1	0–3
86	M	31	99	44.9	0.5	0	96	180	1:1	2	Negative	0.0	0–3
Average		52	156.8	71.2	3.1	37.2	115	193.8	1:10	4.6	6 negative 3 faint delay	0.22	0–3
Subgroup B-2													
3	M	18	140	63.5	4	133	260	140	1:20	4	Negative	0.4	0
19	M	70	146	66.2	6.5	27	137	140	1:10	6	Faint delay	0.4	0
66	M	39	160	72.6	5	35	251	160	1:10	8	Faint delay	0.5	0
87	F	55	131	59.4	1	48	234	200	1:10	8	Faint delay	0.5	0
Average		45.5	144	65.3	4	60.7	220	166	1:12	6.5	1 negative 3 faint delay	0.45	0

Additional average results for subgroup B-1 were: urea nitrogen, 14.4 mg.; carbon dioxide, 52.4; hemoglobin, 13.2 Gm.; Wassermann reactions, negative.

Additional average results for subgroup B-2 were: urea nitrogen, 14.7 mg.; carbon dioxide, 49.5; hemoglobin, 15.1 Gm.; Wassermann reactions, negative.

prior to these tests. Multiple calculi were present in each case. Patient 26 was a woman, 43 years of age, in whom diabetes had been diagnosed three years after operation. At the time of examination she was apparently well and required ten units of insulin and a prescription diet. Patient 62 was a woman, 58 years of age in whom diabetes was diagnosed at the time of operation. This patient had used extremely large doses of insulin for a year previous to the tests. It was necessary to have her under constant observation to prevent acidosis, which was present five times prior to continuous hospitalization. Patient 88 was a woman, aged 65, who entered the hospital with gangrene of the foot, and it was necessary to amputate the thigh. The tests were performed just prior to her departure from the hospital. Patient 92 was a man,

20 years of age, who had advanced pulmonary tuberculosis with cavity formation in both upper lobes. While in the hospital, he gained weight and improved markedly. Patient 97 was a man, aged 41, who had had progressive muscular distrophy for two years and apparently during the past six months had shown some general improvement. Patient 99 was a woman, aged 47, who had used alcohol excessively for several years. She had been treated in the women's psychopathic department for three months prior to her transference to the metabolic wards for study.

The individual data in group B are given in table 1. Patient 17 of this group was an extremely obese woman weighing 309 pounds (140.1 Kg.). In addition to 140 units of insulin, she was taking 2 grains of thyroideum siccum daily. Patient 45 was a woman, aged 42, who

TABLE 2.—*Data on Patients in Group C—Subgroup 1*

Patient	Sex	Age	Weight Lb.	Weight Kg.	Duration of Diabetes, Yr.	Units of Insulin Daily	Blood Dextrose, Mg.	Cholesterol, Mg.	Urobilinogen (Urine Dilution)	Icterus Index	Result, Qualitative van den Bergh Test	Mg. Bilirubin, Quantitative van den Bergh Test	Bromsulphalein Retention, %
5	F	33	106	48.1	1	5	104	190	1:200	100	Immediate	8.0	100
35	M	57	137	62.1	0.25	15	100	195	None	160	Biphasic	20.0	58
56	M	68	130	59	3	15	140	160	1:200	60	Immediate	11.0	70
61	M	49	120	58.5	2	15	129	157	1:100	6	Biphasic	0.2	40
59	M	43	165	74.8	0.5	42	118	125	1:50	6	Negative	0.3	5
69	F	48	150	68	0.5	38	139	120	1:50	5	Negative	0.3	10
98	F	60	137	62.1	2	55	125	160	1:200	6	Negative	0.3	10
50	M	67	129	58.5	2	65	157	...	1:70	6	Negative	0.3	0
12	F	75	138	62.6	1	8	166	135	1:50	2	Negative	0.0	25
13	F	36	134	60.8	1	40	113	160	1:10	4	Negative	0.0	15
90	F	39	133	60.3	1	5	71	170	1:50	4	Negative	0.1	0
Average		52.2	135.1	61.25	1.3	25.7	124.1	157					

Additional average results were: urea nitrogen, 27 mg. (high from three cases of nephritis); carbon dioxide, 49.7; hemoglobin, 12.6 Gm.; albumin present in all specimens of urine; Wassermann reaction, negative in all cases except no. 50.

had an infected finger that was later amputated. She had a leukocyte count of over 10,000 and required 69 units of insulin daily. Patient 86 was a man, aged 31, who had a severe form of xanthoma associated with profound secondary anemia. The hemoglobin was 10.1 Gm. and the erythrocytes 2,300,000. Patient 3 had been in coma five times. He was uncooperative and frequently failed to observe his diet.

The thirty-nine members of group C were placed in two groups. C-1 was composed of eleven patients, seven of whom showed clinical manifestations of hepatic dysfunction, one syphilis and three nephritis. Data on these are given in table 2. C-2 included the remaining twenty-eight patients. Not one of these afforded clinical evidence (except laboratory) of hepatic injury. It was impossible to demonstrate any complicating factor that could influence the tests for hepatic function. For data concerning these patients, see table 3.

In group C-1, the case of patient 5 was diagnosed as catarrhal jaundice. This condition appeared four months after the removal of infected teeth and tonsils, which was done with the hope of improving the diabetic condition. The selected tests were done frequently, and there was gradual improvement. She was discharged four weeks after hospitalization and six weeks after the onset of jaundice. At this time, urobilinogen was present in a dilution of 1 : 50; there was bromsulpha-

TABLE 3.—*Data on Group C—Subgroup 2*

Patient	Sex	Age	Weight Lb.	Weight Kg.	Duration of Diabetes, Yr.	Units of Insulin Daily	Blood Dextrose, Mg.	Cholesterol, Mg.	Urobilinogen (Urine Dilution)	Icterus Index	Result, Qualitative van den Bergh Test	Mg. Bilirubin, Quantitative van den Bergh Test	Bromsulphalein Retention, %
4	M	61	158	71.7	5	0	93	180	1:20	6	Negative	0.3	5
22	M	52	165	74.8	1.5	30	96	180	1:20	4	Negative	0.2	5
42	F	58	135	61.2	3	45	158	160	1:10	6	Faint delay	0.3	8
44	F	46	131	59.4	1	69	185	155	1:20	4	Negative	0.1	3
51	F	60	135	61.2	?	37	141	200	1:10	4	Negative	0.1	3
52	F	53	88	39.4	3	57	109	242	1:20	5	Negative	0.2	8
72	M	37	138	62.6	1	54	178	160	1:10	4	Faint delay	0.2	10
73	M	74	130	59	0.5	30	169	200	1:10	4	Faint delay	0.2	8
75	F	73	134	60.8	16	8	140	150	1:1	4	Faint delay	0.2	3
76	F	70	134	60.8	2.5	120	237	210	1:10	6	Negative	0.3	3
77	M	68	144	65.3	5	5	105	185	1:10	4	Negative	0.1	3
83	F	64	115	52.1	1	60	257	180	1:10	4	Negative	0.1	3
84	M	61	98	44.5	1	40	144	165	1:20	5	Faint delay	0.3	5
85	F	52	145	65.8	1	40	132	190	1:20	4	Negative	0.2	8
91	F	61	140	63.5	1	76	183	150	1:20	6	Negative	0.3	5
94	M	65	118	53.5	1	8	97	160	1:10	4	Negative	0.0	13
41	M	54	165	74.8	7	10	122	155	1:10	8	Negative	0.4	5
54	M	53	179	81.2	1	15	118	180	1:20	6	Negative	0.5	5
18	M	49	148	67.1	3	15	183	165	1:50	12	Faint delay	0.7	25
34	M	62	136	61.7	1	3	104	165	1:50	8	Faint delay	0.5	10
82	M	67	134	60.8	7	20	133	175	1:50	10	Faint delay	0.6	3
10	M	54	198	89.8	2	40	143	135	1:50	5	Faint delay	0.5	0–3
24	M	28	119	54	1	25	118	150	1:50	8	Faint delay	0.5	0–3
70	M	70	103	46.7	2	3	142	140	1:50	10	Faint delay	0.5	0–3
7	M	52	126	57.2	7	39	183	240	1:50	12	Faint delay	0.5	0
11	M	43	129	58.5	3	35	278	160	1:100	4	Faint delay	0.3	0
30	M	40	126	57.2	2	20	260	170	1:50	8	Negative	0.3	0
67	M	42	115	52.1	10	27	152	165	1:50	6	Negative	0.2	0
Average			52.2	133	60.3	3.3	31.5	159.7	173.3	1:28	6	15 negative 13 faint delay	0.3	5.5

Additional average results were: urea nitrogen, 14.2 mg.; carbon dioxide, 51.8; hemoglobin, 13.3 Gm.; Wassermann reactions, all negative.

lein retention, 20 per cent; the icterus index was 60; the van den Bergh reaction was biphasic and showed 3 mg. of bilirubin; there was 190 mg. of cholesterol.

Patient 35 was a man who had been in good health and apparently free from diabetes. He gave a history of symptomless jaundice which had been gradually increasing for three months. At this period, he entered the hospital, and it was found that 15 units of insulin were necessary to control the hyperglycemia. The various tests were performed frequently. There was a total absence of urobilinogen, both in urine and in duodenal contents, at all times. The last bromsulphalein test showed 65 per cent retention; the icterus index was 100; the van den

Bergh reaction was biphasic, and showed 10 mg. of bilirubin. An exploratory operation showed an extensive carcinoma of the pancreas, causing complete occlusion of the biliary passages. The autopsy four weeks later corroborated the operative diagnosis.

Patient 56 was a man who had had diabetes for over three years. He entered the hospital on account of a severe nasal hemorrhage. He then also afforded clinical evidence of portal cirrhosis. It was necessary to perform paracentesis abdominalis three times. He gradually improved, and when discharged showed: urobilinogen, 1:20; bromsulphalein retention, 35 per cent; icterus index, 25, and van den Bergh reaction, biphasic, and showed 1.5 mg. of bilirubin.

Patient 61 was unusually interesting. Eleven years before these studies, he entered the Philadelphia General Hospital with anasarca, and a diagnosis of alcoholic cirrhosis was made. He improved. Three years before these tests diabetes developed. In January, 1929, he had an amputation of the thigh for gangrene of the foot and leg. He improved and was discharged to the metabolic clinic. Jaundice first appeared on July 1, 1929. At this time, there was no urobilinogen in the urine, and the van den Bergh reaction was an immediate direct reaction, with 21 mg. of bilirubin. Daily examinations showed little change until the sixth day, at which urobilinogen could be detected in undiluted urine. The van den Bergh test showed 15 mg. of bilirubin. On the twelfth day, urobilinogen was present in a dilution of 1:20. The van den Bergh reaction was biphasic, with 15 mg. of bilirubin. On Aug. 2, 1929, Talma's operation was performed and a section of the liver removed for study. The pathologic report was: adenoma of the parenchyma of the liver. On October 22, urobilinogen was present, 1:100; there was 40 per cent retention of bromsulphalein; the icterus index was 6; the van den Bergh reaction, direct, was negative; indirect, 0.2 mg. On Jan. 7, 1930, the urobilinogen was present in a dilution of 1:10; there was 20 per cent retention of bromsulphalein; the icterus index was 8; the van den Bergh reaction was very faintly biphasic, with 0.3 mg. of bilirubin. At this time, the patient was clinically improved.

Patient 59 was a man who had been using alcohol to excess for at least two years prior to entering the hospital. The liver was palpable and definitely enlarged. He also had oral sepsis and peripheral neuritis of the right foot and leg. Treatment directed toward his diabetic condition caused a gradual improvement. At the end of ten weeks, he was apparently normal, except for diabetes mellitus.

Patient 69 was a woman who entered the hospital for gallbladder disease associated with jaundice. The diabetic condition was discovered prior to operation, at which carcinoma of the liver and biliary tract was

diagnosed. Drainage was instituted, but the patient gradually succumbed. Death was undoubtedly hastened by multiple abscesses of the back.

Patient 98 was a woman who seven years previously had an amputation of the breast because of carcinoma. Four years later, diabetes developed, which required 55 units of insulin daily. She returned to the hospital in December, 1929, on account of marked dyspnea. Physical signs suggested carcinoma of the lungs. This diagnosis was supported by roentgenograms, and also by the removal of a sanguineous pleural effusion. She felt improved and insisted on leaving the hospital. Death occurred shortly thereafter, but it was impossible to obtain permission for an autopsy. Probably the liver also contained metastatic carcinoma.

Patient 50 had a severe grade of diabetes. A year previously gangrene of the foot and leg necessitated amputation of the thigh. The patient had a four plus Wassermann reaction and furnished evidence permitting the diagnosis of tabes dorsalis.

Patient 12 had a severe nephritis in addition to diabetes. The bromsulphalein and urobilinogen tests both yielded positive results. The erythrocytes were 2,500,000; the leukocytes, 12,500. The hemoglobin content was 7.8 Gm. Death occurred forty-eight hours after admission to the hospital.

Patients 13 and 90 also were nephritic. Studies of the liver were conducted at least two months after hospitalization. At this time, the condition of the kidneys had markedly improved, and the diabetes was well controlled. Patient 13 had the severer type of diabetes, and patient 90 showed greater renal dysfunction. The hemoglobin readings were 11.5 and 11.8, respectively. It is interesting to note in this connection that the van den Bergh readings were lower than normal in all of these nephritic persons with secondary anemia.

The members of subgroup C-2 require only brief comment. They were all well standardized and apparently free from complications at the time of examination. Seven patients, nos. 18, 51, 70, 75, 77, 84 and 94, entered the hospital with gangrenous feet and legs, and it was necessary to perform unilateral amputations of the thigh. These patients all improved rapidly, but none of them was studied until recovery was practically complete.

Patient 11 was jaundiced for seven months about four years before these studies. He was finally referred to the metabolic department with the diagnosis of diabetes mellitus and carcinoma of the liver. Under a strict diabetic regimen, he apparently returned to normal (except for diabetes) and has been able to work continuously as a hospital orderly for over three years. It seems justifiable to assume that the diagnosis of carcinoma was an erroneous one.

COMMENT

The forty-eight members of group A offered neither clinical manifestations nor laboratory evidence of hepatic dysfunction. It was expected that the studies of hepatic function in three of the cases (that of the alcoholic person and the two of patients who had cholecystectomies) would give positive observations, but these remained within a normal range. Undoubtedly, the great size of the liver at all ages amply provides for the numerous hepatic functions, and also affords a "factor of safety" sufficient to care for a considerable degree of injury, thus making the estimation of minimal hepatic dysfunction an unusually difficult problem. It seems reasonable to assume that any evidence of damage to the liver when obtained by approved tests, carefully performed, should be considered of diagnostic import. In addition, these studies were all conducted on patients using accurately weighed prescription diets. All were fairly well standardized, and in group A all but one required insulin. Jones, Castle, Mulholland and Bailey [8] concluded that the better the diabetes is controlled the less apparent hepatic dysfunction becomes. This coincides with the impression gained in this series. Undoubtedly, the rigidly enforced regimen (embracing as it does a well balanced, nutritious diet, rich in vitamins, minerals and base-producing foods, insulin as required, proper rest and exercise, and general prophylactic and hygienic measures) contributes in a great measure toward hepatic regeneration and the restoration of normal function.

In group B, the retentions of bromsulphalein, even though extremely slight, might be considered sufficient data to classify these patients as having hepatic dysfunction. As the amount of dye retained could not be accurately measured, these patients, as well as those with only the slightly elevated van den Bergh readings, will not be considered as showing definite hepatic dysfunction, but are presented merely for consideration.

The thirty-nine patients in group C all furnished laboratory data interpretable as evidence of hepatic dysfunction. As the purpose of the investigation was to determine hepatic function in relation to diabetes, eleven of these were excluded. Seven had definite manifestations of injury to the liver, the clinical diagnosis being: catarrhal jaundice, carcinoma of the pancreas, adenoma of the liver, portal cirrhosis, alcoholic cirrhosis, metastatic carcinoma of the lungs and liver and carcinoma of the liver, respectively. Three others had a severe grade of nephritis and another syphilis.

The twenty-eight patients selected from group C afforded no clinical manifestations of hepatic dysfunction, and it was impossible to determine any complicating factor besides diabetes, which could in any way influence the tests for hepatic function. These patients apparently furnish

an index of hepatic function in patients well treated for diabetes mellitus. They were found to be older, to be only slightly heavier and to have a history of longer duration than the members of group A. The average value of the blood sugar during fasting was higher, the insulin requirement practically identical and the cholesterol readings somewhat lower.

If 0.3 mg. is taken as the high normal for the van den Bergh reading, it is less delicate than the bromsulphalein test. It exceeded 0.3 mg. in nine cases. As noted by other investigators, secondary anemia tends to produce a hypobilirubinemia.

TABLE 4.—*Summary of Data on Groups A, B, C-1 and C-2*

	Group A	Group B	Group C-1	Group C-2
Patients	48	13	11	28
Sexes	25 M, 23 F	7 M, 6 F	5 M, 6 F	19 M, 9 F
Average age, yr.	49.5	50.1	52.2	52.2
Average weight, lb.	131.8 (59.8 Kg.)	152.7 (69.3 Kg.)	135.1 (61.25 Kg.)	133 (60.3 Kg.)
Average duration of illness, yr.	2.7	3.3	1.2	3.3
Average insulin units	33.3	41.5	25.7	31.5
Average blood dextrose, mg.	142.4	147.3	124.1	159.7
Average urea nitrogen, mg.	14.8	14.5	27	14.2
Average cholesterol, mg.	188.2	183.2	157	173.3
Average carbon dioxide	51.4	51.5	49.7	51.8
Average hemoglobin, Gm.	13.5	13.7	12.6	13.3
Wassermann reactions	All negative	All negative	10 negative, 1 positive	All negative
Average urobilinogen dilution	1:14	1:11	1:105	1:28
Average icterus index	5.7	5.2	35.5	6
Results, qualitative van den Bergh test	5 faint delay 43 negative	6 faint delay 7 negative	2 biphasic 2 immediate 6 negative	13 faint delay 16 negative
Average quanitative van den Bergh test	0.17	0.29	4–1	0.30
Average bromsulphalein retention, %	0	0–3	29.8	5.4

In group A, liver function tests all gave normal results.

In group B, liver function tests all gave normal results, except possibly nine cases with from 0 to 3 per cent bromsulphalein retention and tow cases with van den Bergh results of 0.4 mg. and two with 0.5 mg.

In group C-1, liver function tests (one or more) gave definitely positive results. These cases all presented demonstrable complications (seven clinical disease of liver, three nephritis, and one syphilis).

In group C-2, liver function tests (one or more) gave definitely positive results. These cases presented no demonstrable complications or any clinical manifestations of disease of the liver. All were standardized.

The icterus index was found to be subject to greater personal error than the van den Bergh test. It was of value only when the serum was free from hemolysis, and the results more nearly paralleled the van den Bergh readings when the phosphate buffer was used for dilution. It was greater than 6 in eight cases.

The urobilinogen test was found to be convenient, simple, practically free from personal error, nontime-consuming and of no annoyance to the patient. It gave a result exceeding 1 : 20 in ten cases, and 1 : 10 in eighteen cases.

The bromsulphalein test usually showed some retention. It was free from prolonged discomfort or hazard and easily performed. It was found to give definitely positive results in twenty-one cases, and questionably positive results (from 0 to 3 per cent) in three cases in which

the urobilinogen and quantitative van den Bergh tests suggested hepatic dysfunction. The four others presented no retention of dye, but all showed an increase of urobilinogen. Probably in one of these cases there was also an abnormal reading for serum bilirubin, but in the remainder the results were within the normal range.

Apparently in the case of standardized diabetic patients, the bromsulphalein test will be found to give a positive result most frequently. In the study of hepatic function, it seems advisable to conduct a series of complementary tests for the estimation of this function and to correlate carefully the clinical data before attempting their interpretation.

The cholesterol readings exceeded 170 mg. in twelve cases, but it was impossible to explain the significance of this elevation as related to hepatic function.

The data for groups A, B, C-1 and C-2 are found in table 4.

CONCLUSIONS

1. Clinical and laboratory studies apparently indicate that hepatic dysfunction is a frequent occurrence in diabetes mellitus. Of the cases studied, 7 per cent showed both clinical and laboratory evidence of hepatic dysfunction, 28 per cent furnished only laboratory data, 48 per cent were without any abnormal indications and an additional 13 per cent gave only minimal or doubtful readings.

2. The older the patient and the longer the diabetes mellitus remains uncontrolled, the more frequently hepatic dysfunction becomes demonstrable.

3. Even though the bromsulphalein test was found to yield positive results most frequently, it seems advisable to conduct a series of complementary tests.

4. The study of these cases over an extended period of time created the impression that the modern diabetic regimen materially aids in improving hepatic function and in conjunction with proper preoperative and postoperative treatment permits even diabetic patients with clinical manifestations of hepatic dysfunction to undergo major surgical operations with comparative safety. This study also showed that any patient in whom hepatic dysfunction is demonstrated might advantageously be placed on a prescription diet and a careful search instituted for evidence of latent or potential diabetes.

INSUFFLATION OF COMPRESSED AIR IN THE TREATMENT FOR PNEUMONIA*

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In a previous study[1] it was noted that in the dog an increased intrapulmonic pressure would result in interstitial emphysema, acute pneumothorax, pneumoperitoneum and air embolism. It was found that air injected intrabronchially under increased pressure had little or no effect if a good outlet for it was supplied. If, on the other hand, there was an insufficient outlet or a complete blocking of the outflow of air, the lung expanded when the intrabronchial pressure was raised between 20 and 35 mm. of mercury. When the pressure reached a point between 60 and 100 mm. of mercury, invariably, the dogs showed the syndrome of interstitial emphysema, pneumothorax, pneumoperitoneum and air embolism. These results were obtained in dogs with normal and also with pneumonic lungs.

We have repeatedly noticed that the pulmonary vessels can be emptied easily by increasing the alveolar pressure. In fact, after severing the heart from its connections with the pulmonary vessel, we have been able to wash out all the blood from the pulmonary vessels by allowing the inflow of compressed air into the lung. The pressure at which this air was blown into the lungs was just high enough to distend them to their optimum volume, but not to distend them to the point of maximum drumlike distention. Under such conditions after the air was allowed to flow for a few minutes, it was noticed that blood oozed slowly from the severed ends of the pulmonary vessels, and eventually only air came through. When this point was reached, a surface stereomicroscopic study of the lung showed a complete replacement of the blood by air in the smaller as well as in the larger vessels. By filling the alveoli with a fixing solution and then blowing air under these conditions, we have been able to force this fluid from the alveoli into the pulmonary circulation without any apparent gross or microscopic injury to the alveolar wall.

AIR EMBOLISM

The phenomenon of air embolism is probably more frequent than is generally supposed. We have repeatedly noticed air finding its way

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* From the Department of Surgery, College of Medicine, University of Illinois.

1. Joannides, M., and Tsoulos, G.: Experimental Production of Interstitial Emphysema and Air Embolism, Arch. Surg. **21**:333 (Aug.) 1930.

into the pulmonary vessels of the frog when the animal struggled sufficiently during the normal expansion of the lung to cause an increased intrapulmonic pressure. Undoubtedly the reason why the phenomenon is not recognized clinically is that small amounts of air in the circulation are well borne, but large amounts, injected over a short period of time, reaching the heart and finally some vital area of the brain, cause shock or transitory hemiplegia. The so-called pleural shock produced during the induction of artificial pneumothorax has been definitely shown by Van Allen and his associates to be related to air embolism.[2]

When a large amount of air reaches the heart, it comes in contact with the blood, which is a colloidal solution and has a tendency to emulsify much in the same manner as soap, so with each cardiac contraction the blood is broken up into smaller and smaller air bubbles, and the animal dies of anoxemia and asphyxia. Some of this emulsified blood finds its way into the general circulation and there it can be identified as air bubbles all along the course of the vessels. A good method for determining the presence of air in the circulation is to insert a needle of a wide gage into the vein, and, as the blood is sucked into a syringe, air bubbles, if present in the vein, will be visible in the syringe. A more accurate method of searching for bubbles in the smaller vessels and capillaries is by means of a capillary microscope.

Since it is easy to squeeze fluids into the pulmonary circulation under normal conditions, we decided that it might be of value to try this method in the treatment of pneumonia. In this disease it is evident that the exudates that are produced in the alveolar wall follow the path of least resistance and drain into the alveolar sac.[3] In pneumonia, regardless of the etiology or the severity we found that the steps in the development and course of the disease are no different than those in acute inflammation elsewhere in the body. The differences presented are those due to the peculiar structure of the lung.[4]

CARDIOCIRCULATORY COMPENSATION IN PNEUMONIA

The lung is a very vascular organ, and the flow of the blood in the pulmonary vessels depends, among other things, on the intermittent

2. Van Allen, C. M.; Hrdina, L. S., and Clark, J.: Air Embolism from Pulmonary Vein: Clinical and Experimental Study, Arch. Surg. **19**:567 (Oct.) 1929.

3. Joannides, M., and Steinman, F.: The Mechanism of Pneumonia, Arch. Int. Med. **47**:24 (Jan.) 1931.

4. A detailed discussion appears in the article by M. Joannides and F. Steinman (footnote 3).

expansion and contraction of the lung tissue. When the lung becomes immobilized by external compression or internal drowning with exudate, it becomes fairly solid and loses its elasticity, so that little or no air enters and leaves the lung during inspiration and expiration. This immobilization of the lung has a definite effect on the circulation and the oxygen carrying capacity of the blood. The circulation becomes impeded, the heart suffers from overwork and asphyxial changes, so that sooner or later the patient collapses because of the cardiac and circulatory decompensation. In other words, in pneumonia, the patient needs a proper cardiocirculatory compensation, a proper supply of oxygen and the elimination of waste products accumulating in the blood stream as a result of asphyxia.

We noticed experimentally that the circulation in normal dogs suffers definite changes coincident with the production of an open pneumothorax. Under normal conditions the record of blood pressure in a dog, obtained by direct connection with the femoral artery, shows definite respiratory waves. These waves promptly disappear with the production of open pneumothorax, and if artificial respiration is not instituted, the amplitude of the wave becomes gradually shorter, eventually reaching a pulse pressure of almost zero. At this point frequently (for some reason as yet unexplainable) the blood coagulates in the cannula. If the animal is let alone, the systolic pressure takes a sudden drop much in the manner of the blood pressure in an animal dying from an overdose of chloroform. The heart at this point also shows a definite and quite constant bradycardia before it finally stops beating. If such an animal is treated by means of artificial respiration at any stage of the cardiocirculatory collapse, the normal respiratory waves are again apparent in the record of the blood pressure, and the animal may be kept alive for as long as it is desired. In the late stages of cardiac collapse, in which asphyxial bradycardia occurs just before the heart finally stops beating, it is necessary that artificial respiration be established. When artificial respiration is instituted, it is quite necessary that the flow of compressed air in the lungs be intermittent, and there should be a sufficient blocking of the outflow of air in the system of tubing to increase the intrapulmonic pressure to a point between 20 and 35 mm. of mercury for the dog. The blocking of the outflow must be complete and just long enough so that the desired pressure is obtained. The expanded lung thus fills up the thoracic cavity, and at the same time causes a slight bulging in the wall of the chest at the costal margin and in the anterior abdominal wall. For measuring intrapulmonic pressure we have used a diaphragm

air pressure indicator furnished by Dr. A. Littig,[5] chief anesthetist of the Illinois Research and Educational Hospitals.

It is obvious to those who do much work under artificial respiration that it is not necessary to use either pure oxygen or oxygen mixed with carbon dioxide. Such a provision, at least in the experimental animal has been found unnecessary and expensive. Ordinary compressed air has a sufficient amount of oxygen to take care of the asphyxia. The increased pressure, on the other hand, under proper management, allows for sufficient expansion and contraction of the lung to reinforce the heart and the circulation.

In pneumonia, a disease in which consolidation results from the drowning of the alveoli and the edema of the interalveolar wall, the use of positive pressure in artificial respiration theoretically would be of definite benefit. The increased intrapulmonic pressure (from 20 to 35 mm. of mercury) will help to stretch and contract the interalveolar wall. It will also aid in squeezing some of the exudate from this wall into the circulation because the interalveolar pressure is now higher than the pressure of the blood in the pulmonary vessels. Moreover, some of the exudate in the alveolar space will find its way into the circulation. Finally, the lung will get sufficient oxygenation to take care of the anoxemia and asphyxia. We tried this method in dogs when the animal was dying from pneumonia. It was noticed that an animal so weak physically that one could barely see the respiratory movements, and to all appearances almost dead, began to breathe normally after artificial respiration was established for from one to five minutes, and continued to do so for a period of from ten minutes to an hour before it again showed signs of collapse. The rate of obstructed outflow was from 20 to 30 times per minute, and the intrapulmonic pressure varied from 20 to 35 mm. at the peak and from 5 to 10 mm. of mercury when the outflow of air was completely open.

The anatomic changes that occurred in the pneumonic lung are of interest. When the intra-alveolar pressure was increased in the dog to a point between 20 to 35 mm. of mercury the liver-like, dark-colored, consolidated lung began to expand and to present a crepitating appearance and the color became pinkish red, but the vessels still stood out prominently. When the lung was allowed to collapse it was no longer solid, but showed crepitation and a less purple color. Microscopically, this lung showed alveolation just like that in the normal lung, but definite changes in the alveolar surface and in the wall still persisted.

5. Littig, A.: Measurement of Positive Pressure Used in Gas Anesthesia, Wisconsin M. J. **28**:217 (May) 1929; Anesth. & Analg. **9**:82 (March-April) 1930.

TECHNIC

A brief description of the technic in the administration of the compressed air may be of value.

The compressed air obtained from a tank is connected to an air-tight mask by means of rubber tubing. This tubing, by the use of T or Y glass or metal tubings, provides for an outlet and also for the connection to the Littig manometer.[6] One provision is essential, namely, that the diameter of the tubing at the outlet of air should be the same, or even greater, than the diameter of the tubing attached to the mask. For the mask, half-inch tubing is best. For the attachment to the Littig manometer, a tubing one-fourth inch in diameter is sufficient. The compressed air is now allowed to run into the lungs of the animal, and the pressure is adjusted to a point of 5 or 10 mm. of mercury with the outflow completely open. The outflow is now completely closed with the finger until the animal shows a bulge in the anterior abdominal level and at the costal margin. This occurs coincidentally with the rise of the intrapulmonic air pressure to from 20 to 35 mm. of mercury. The outflow is now released, and one sees a collapse of the thoracic and abdominal wall. The length of complete closure in the outflow until expansion of the lung takes place varies with the initial pressure. When this initial pressure is high, the expansion occurs faster, and the intrapulmonic pressure varies from 25 to 35 mm. of mercury. Care must be taken not to increase the pressure too long or too high, because the syndrome of interstitial emphysema results.[1] At times the stomach may become greatly distended with air during this treatment. Such distention is distressing to the patient, and it interferes with the respiratory excursion of the diaphragm. It is best treated by the passage of a stomach tube to a point beyond the cardia in which obstruction occurs.[7]

At the present time these studies have been limited to the dog. The exact pressure at which the human lung expands is now being measured. A clinical trial will be made as soon as the optimum pressure is obtained.

SUMMARY

1. Increased intra-alveolar pressure, when excessive, produces interstitial and mediastinal emphysema, pneumothorax, pneumoperitoneum and air embolism.

2. Increased intra-alveolar pressure causes emptying of the pulmonary vessels when severed from the heart.

3. In pneumonia, the alveoli are drowned with exudate coming from the interalveolar wall and the alveolar surface.

4. Cardiocirculatory collapse follows the consolidation and immobilization of the lung, which causes stasis because of the absence of intermittent expansion and contraction.

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6. Littig (footnote 5, first reference).

7. Joannides, M.: Surgery of the Lung: Care of the Stump in Pneumectomy and in Lobectomy, Arch. Surg. **17**:91 (July) 1928; The Relation of the Hiatus Esophageus of the Diaphragm to the Stomach, Arch. Int. Med. **43**:61 (Jan.) 1929.

5. The heart and the circulation improved when intermittent artificial respiration was instituted in pneumonic lungs as well as in open pneumothorax.

6. A pressure of from 20 to 35 mm. of mercury is sufficient to cause complete expansion of the normal as well as of the pathologic lung.

7. Compressed air serves the purpose of artificial respiration safely and inexpensively. It is not necessary to use pure oxygen or a combination of oxygen and carbon dioxide.

8. The outflow of the air is important, because it regulates the degree of pressure in the lung, the amount of air blown in, the degree of lung expansion and the prevention of the interstitial emphysema syndrome.

9. Pneumonic, consolidated, dark-colored lungs when subjected to increased intrapulmonic air pressure either inside or outside of the body became crepitating and pinkish red again.

THE COMPARATIVE CHANGES IN GASTRIC ACIDITY AND URINARY REACTION AFTER THE INJECTION OF HISTAMINE*

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In a previous communication,[1] we discussed the advantages of a test combining analysis of gastric contents with estimation of urinary acidity as a method of obtaining more controlled results in the determination of gastric acidity.

It has been known that persons having relatively normal gastric secretion are prone to have less acid urine after meals, a phenomenon commonly referred to as the "alkaline tide." On the other hand, a relative fixation of the urinary reaction has been shown to exist in patients with true achlorhydria. These observations were recently confirmed by Hubbard and his co-workers [1a] and by Baehr,[2] Davis [3] and others.

We decided to employ histamine as the gastric stimulant in our studies. Histamine has been recognized as the most reliable gastric stimulant for hydrochloric acid by numerous workers, particularly Andresen [4] and Gompertz and Vorhaus.[5] Ackman [6] was particularly interested in studying the relationship between the gastric acidity and the hydrogen ion concentration of the urine after the injection of histamine. It occurred to us to employ this principle of the relationship between the gastric acidity and the true urinary acidity (p_H) in a clinical secretory test with histamine as the gastric stimulant.

METHOD OF PROCEDURE

The patient was requested to urinate at 6:30 a. m., emptying the bladder as completely as possible This was done again at 8:30 a. m., and the hydrogen ion concentration (p_H) of the second specimen was determined immediately.

* Submitted for publication, June 23, 1930.

* From the Gastro-Intestinal Department, Jewish Hospital.

1. Matzner, M. J., and Gray, I.: A Critique of Present Methods for the Study of Gastric Acidity, Arch. Int. Med. **47**:58 (Jan.) 1931.

1a. Hubbard, R. S.; Munford, S. A., and Allen, E. G.: Am. J. Physiol. **68**:207, 1924.

2. Baehr, G.: Bull. New York Acad. Med. **3**:419, 1927.

3. Davis, D. T.: Brit. J. Exper. Path. **10**:1 (Feb.) 1929.

4. Andresen, A. F. R.: Tr. Am. Gastro-Enterol. A., 1926, p. 53.

5. Gompertz, L. M., and Vorhaus, M. G.: J. Lab. & Clin. Med. **11**:14 (Oct.) 1925.

6. Ackman, F. D.: Canad. M. A. J. **15**:1099, 1925.

A Rehfuss tube was passed about 9 a. m., and the contents of the fasting stomach were extracted. The stomach was lavaged with water until a clear return was obtained. Immediately thereafter from 0.25 to 0.5 mg. of histamine was injected subcutaneously. Gastric extractions were made every hour over a period of from three to five hours. The patient was instructed to empty the bladder completely at each urination. The gastric specimens were quantitatively analyzed for free and total acidity.

The hydrogen ion concentration of the urine (p_H) was immediately determined with the Hellige comparator.[7] This method is extremely simple and in contradistinction to other methods lends itself readily to clinical use. The determination can be made in a few minutes.

Care was exercised in this study to prevent errors from variations in the respiratory exchange. The patient was kept as nearly at absolute rest as possible throughout the test. We essentially adopted the practice of Hubbard, Munford and Allen,[1] of accepting as evidence of an alkaline tide a change of p_H of 1 in one specimen or of 0.5 p_H in two specimens. These authors found that if this criterion was accepted, the results of the urinary test failed to agree with the results of the fractional gastric analysis in about 20 per cent of all the determinations carried out.

RESULTS

We employed this method in a study of twenty-five patients. Not more than 50 per cent of our patients who had free hydrochloric acid in the gastric extractions after the injection of histamine had a definite urinary alkaline tide. Our results may be classified as follows:

Group 1: Patients with free hydrochloric acid and definite urinary alkaline tide, 6. In this group, after the injection of histamine, free hydrochloric acid was demonstrated in the extracted gastric specimens, while the development of a definite alkaline tide was shown by the urinary tests.

Group 2: Patients with free hydrochloric acid and no urinary alkaline tide, 6. In this group, free hydrochloric acid was demonstrated in the extracted gastric specimens. However, in contradistinction to the patients of group 1, these patients did not show a definite urinary alkaline tide.

Group 3: Patients with no free hydrochloric acid and no urinary alkaline tide, 12. In this group, free hydrohcloric acid was not demonstrated in the extracted gastric specimens after the injection of histamine. A simultaneous study of the urine showed a relative fixation of the urinary reaction (no alkaline tide).

Group 4: Patients with no free hydrochloric acid and a definite alkaline tide, 1. This patient, J. C., a man, aged 58, was admitted to the gastro-intestinal service of Dr. Irving Gray, with a history of anorexia, gradual loss of weight and progressive dysphagia. The "combined test" showed the following discrepancy: a definite urinary alkaline tide but no free hydrochloric acid in the extracted specimens.

7. The apparatus can be obtained from Eimer and Amend, New York.

In seeking an explanation for the discrepancy between the gastric analysis and the urinary alkaline tide, it was surmised that the Rehfuss tube might be coiled up in the esophagus, owing to an obstruction at its lower end. If this were so, our analyses were esophageal rather than gastric. Immediate fluoroscopic examination with the Rehfuss tube in sutu was done. These examinations definitely demonstrated the Rehfuss tube coiled up in the esophagus. The discrepancy between the gastric analysis and the urinary alkaline tide was thus readily explained.

TABLE 1.—*Results of "Combined Test" in Group 2*

Name	Clinical Diagnosis	Maximum Gastric Acidity: Free HCl	Maximum Gastric Acidity: Total Acidity	p_H of Urine			
J. L.	Neurosis.....	60	70	9:30 a.m. p_H 5	10:10 a.m. p_H 5	11 a.m. p_H 5	12:30 p.m. p_H 4.8
K. B.	Duodenal ulcer?..	18	24	9 a.m. p_H 4.8	9:55 a.m. p_H 5	11:05 a.m. p_H 5	12 m. p_H 5
A. F.	Duodenal ulcer...	70	79	9:30 a.m. p_H 5	10:30 a.m. p_H 5	11:15 a.m. p_H 5	2 p.m. p_H 5.2
J. S.	Neurosis.....	11	18	9:40 a.m. p_H 5	10:30 a.m. p_H 5	11:45 a.m. p_H 5.2	2 p.m. p_H 5.2
B. D.	Duodenal ulcer...	73	78	9:15 a.m. p_H 5	10:15 a.m. p_H 5	11 a.m. p_H 5	12:30 p.m. p_H 4.8
C. D.	Neurosis.....	30	34	9:15 a.m. p_H 7.2	10:15 a.m. p_H 7.2	11:25 a.m. p_H 7.4	12:30 p.m. p_H 7

TABLE 2.—*Results of "Combined Test" in the Case of J. C.*

Time	Gastric Analysis: Free HCl	Gastric Analysis: Total Acidity	Urinary p_H
9:30 a.m.	0	2	5.2
10:00 a.m.	0	4	5.2
10:30 a.m.	0	2	6.8
11:30 a.m.	0	4	6.8

COMMENT

Not more than 50 per cent of the patients in whose gastric extractions we were able to demonstrate free hydrochloric acid after the subcutaneous injection of histamine had a definite urinary alkaline tide. Several considerations suggest themselves to explain this apparent discrepancy. First, it is known that histamine causes an increased secretion of bile and of alkaline intestinal juices. This simultaneous alkaline intestinal secretion might be sufficient at times to offset or to neutralize the effect of the secretion of hydrochloric acid into the stomach. Second, while the stimulus of histamine for gastric secretion is maximum, it is usually not of long duration. The total quantity of

hydrochloric acid secreted may thus not always be sufficient to cause an appreciable change in the urinary reaction.

Kauders, Porges and Essen [8] drew attention to a group of patients with hypersecretion (Reichmann's disease), who in their opinion are less apt to have an alkaline tide after a test meal, because their gastric acidity values are practically maximum throughout the day and less likely to rise appreciably after a test meal.

Hubbard [9] recently emphasized that the investigation of the urinary alkaline tide should be done several hours after the patient's waking. The liberation of the carbon dioxide stored up during the night might be sufficient in itself to exert an influence on the urinary reaction. We have taken this precaution in our studies.

We gained the impression from Ackman's [6] studies that his patients also received breakfast on the morning that histamine was injected. Of course if that were so, a satisfactory explanation would be at hand for the greater percentage of urinary alkaline tides reported in his comprehensive investigation of the effect of histamine on the urinary alkaline tide.

The fact that not more than 50 per cent of our patients in whose gastric extractions free hydrochloric acid was demonstrated after the subcutaneous injection of histamine had a definite urinary alkaline tide led us to abandon histamine as the gastric stimulant in the "combined test." We are employing bouillon (one Steero cube in a cup of warm water) at present, and our results will be published in a subsequent paper.

SUMMARY

1. The advantages of a test combining gastric analysis and estimation of urinary acidity (alkaline tide) are discussed.

2. Histamine was employed as the gastric stimulant.

3. Not more than 50 per cent of the patients in whose gastric extractions free hydrochloric acid could be demonstrated after the injection of histamine had a definite urinary alkaline tide.

4. The use of histamine as the gastric stimulant in studies of the urinary alkaline tide has been discontinued More favorable experiences with Steero bouillon as the gastric stimulant in our studies of the urinary alkaline tide will be reported in a subsequent paper.

8. Kauders, F.; Porges, O., and Essen, H.: Deutsche med. Wchnschr. **47**: 1415 (Nov. 24) 1921.

9. Hubbard, R. S.: J. Biol. Chem. **84**:191 (Oct.) 1929.

NORMAL VARIATIONS IN ERYTHROCYTE AND HEMOGLOBIN VALUES IN WOMEN*

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Red blood cell counts and hemoglobin determinations have been thought by some investigators to fluctuate but little in an individual during the day and by others to show large variations. As it is important to know whether isolated counts should be considered in relation to the time of day of the count and the activity of the person, this study was initiated to determine the variations of erythrocytes and hemoglobin values during short periods of time. It was found that with accurate technic, the red blood corpuscles and the hemoglobin determinations remain remarkably constant during the day, and that there are no significant changes due to rest, moderate activity or food. Real differences may occur, however, between counts for separate days and between averages for longer periods of time

TOTAL COUNTS OF ERYTHROCYTES

Technic.—The inaccuracy that may attend blood counting has invalidated many experiments in which this technic has been used. Krumbhaar [1] (1928) stated that there are sixteen sources of error in making total counts which "if all were cumulative might easily produce a total error of more than 40 per cent without any one item passing a reasonable 'limit of error'". In European hematologic work simple statistical methods have been used to aid in testing the accuracy of the technician and to determine the significance of results, but in this country only a few of the more recent papers have treated data in this way (table 1).

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1. Krumbhaar, E. B., in Cowdry, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1928, p. 284.

Because it seemed necessary to have some definite procedure by which the accuracy of the technician could be tested, the following method has been used throughout this investigation: First each operator counted the cells in 10 or 20 drops from the same pipet until the coefficient of

TABLE 1.—*Determinations of Error Inherent in the Technic*

Author	Date	Coefficient of Variation, per Cent	Method
Vierordt, K.: Arch. f. physiol. Heilk. **11**: 868, 1852	1852	2.36	9 series, 30 counts different days
Welcher, H.: Prag. Vrtljschr. f. d. prakt. Heilk., 1854, p. 25	1854	1.89	2 series, 14 counts
Reinert, E.: Die Zählung der Blutkörperchen und deren Bedeutung für diagnose und Therapie, Leipzig, F. C. W. Vogel	1891	2.97 3.00	5 drops from the same pipet sufficiently accurate value
Bürker, K.: München. med. Wchnschr. **59**: 89, 1912	1912	1.8	7 consecutive days, 4 times 80 squares each day
Jorgensen, G.: Ugesk. f. læger **75**: 1753, 1913	1913	2.5	
Terhola, L.: Arch. f. Gynäk. **103**: 115, 1914	1914	2.9 3.4	For single determinations 9 series, 41 counts
Bing, H. I.: Ugesk. f. læger **81**: 1483, 1919	1919	2.3	
Craandyk, M. M.: Folia haemat. **23**: 11, 1918-1919	1918-1919	3.1; 3.4	6 days, 7 duplicate counts
Hansen, K. M.: Ugesk. f. læger **81**: 1281, 1919	1919	1.73; 2.17	
Bierring, K.: Ugesk. f. læger **82**: 1445, 1920	1920	3.2	
Feucht, B.: Arch. f. d. ges. Physiol. **187**: 139, 1921	1921	1.48	30 counts within 5 days
Emerson, C. P.: Clinical Diagnosis, Philadelphia, J. B. Lippincott Company	1921	estimated 2.0 4.0	In counting includes physiologic variations
Mayers, L. H.: Arch. Int. Med. **30**: 478 (Oct.) 1922	1922	0.2 4.75	5 counts in 7 hours 7 consecutive days
Rud, E. J.: Acta med. Scandinav. **57**: 142, 1922-1923	1922-1923	1.18 to 2.63	10 determinations, 3 series
Brandt, T.: Folia haemat. **32**: 177, 1926	1926	2-3	10 determinations
Lasch and Billich: Ztschr. f. d. ges. exper. Med. **48**: 651, 1925-1926	1926	2.6	6 drops same mixture
Osgood, E. E.: Arch. Int. Med. **37**: 685 (May) 1926	1926	3	Maximum experimental error
Ponder and Millar: Quart. J. Exper. Physiol. **19**: 145, 1928	1928	5	Maximum experimental error

variation was at least less than 3 per cent. Then 10 or 20 drops from each of two pipets from the same drop of blood were counted until the difference between the two means was considered insignificant according to its probable error. Previously it has been thought that successive drops from the same pipet would not have the same cell content because the air bubbles present would have influenced the distribution of the

cells (Komocki,[2] 1924). In this work little difference was found between successive drops when accurate manipulation has been attained. Successful results were obtained only after repeated practice periods, the length of time depending on the person.

For the definition of terms and for the formulas and their use, reference may be made to any of the standard textbooks on statistical methods, but it seems desirable to specify the few used in this work.

a = arithmetical mean or average

d = deviation of an item from the mean

n = number of items

$$\text{standard deviation} = \sqrt{\frac{\text{sum of } d^2}{n}} = \sigma$$

$$\text{coefficient of variation} = \frac{\text{standard deviation}}{\text{mean}} \times 100$$

$$\text{probable error of mean} = \underset{\text{small n}}{\frac{0.6745\sigma}{\sqrt{n-1}}} \qquad \underset{\text{large n}}{\frac{0.6745\sigma}{\sqrt{n}}}$$

$$\text{probable error of standard deviation} = \frac{0.6745\sigma}{\sqrt{2(n-1)}} \qquad \frac{0.6745\sigma}{\sqrt{2n}}$$

$$\text{probable error of coefficient of variation} = \frac{0.6745 \text{ c.v.}}{\sqrt{2(n-1)}} \qquad \frac{0.6745 \text{ c.v.}}{\sqrt{2n}}$$

The value of the method presented in table 2 as a measure for testing the accuracy of the technician either in the training of new workers or in the verifying of the exactness of old workers who have had long or short interruptions can be seen by examining the results obtained by technicians A and D in table 3. Technician D had done no blood counting until two weeks previous to the series reported here, and within that time her efficiency increased steadily. As her operations became more exact, the distribution of cells became more even and the coefficient of variation correspondingly less. This procedure may be applied to work involving total white counts and hemoglobin determinations.

In summary, the following statements may be made concerning the advantages of applying simple statistical methods to the appraisal of technical efficiency in blood counting:

1. The coefficient of variation for the cells counted from one pipet has a definite meaning. It is the measure of the distribution of the cells after the pipet has been filled. In red counts a coefficient of from

2. Komocki, W.: Ueber die Zahl der roten Blutkörperchen bei gesunden erwachsenen Menschen, Virchows Arch. f. path. Anat. **253**:386, 1924.

TABLE 2.—*Method of Determination of the Coefficients of Variation and of the Significance of the Difference Between Two Pipets (Ten Counts from Each)* *

Pipet D3

		d	d^2
1	431	+8	64
2	425	+2	4
3	415	−8	64
4	420	−3	9
5	427	+4	16
6	427	+4	16
7	425	+2	4
8	426	+3	9
9	422	−1	1
10	417	−6	36
		+23 −18	223

$$d' = \frac{+23 - 18}{10} = \frac{5}{10} = 0.5$$

$$\sigma = \sqrt{\frac{\text{sum of } d^2}{n} - d'^2} = \sqrt{\frac{223}{10} - 0.25} = 4.7$$

$$\text{Probable error of a} = \frac{0.6745\sigma}{\sqrt{n-1}} = \frac{0.6745\ (4.7)}{3} = 1.056$$

$$\text{Probable error of } \sigma = \frac{0.6745\,\sigma}{\sqrt{2\ (n-1)}} = \frac{0.6745\ (4.7)}{4.2} = 0.754$$

$$\text{Probable error of c. v.} = \frac{0.6745 \text{ c. v.}}{\sqrt{2\ (n-1)}} = \frac{0.6745\ (1.1)}{4.2} = 0.176$$

a = 423 + 0.5 = 423.5 ± 1.056
σ = 4.7 ± 0.754
c. v. = 1.1% ± 0.2%

Number of cells in a cubic millimeter = × 10,000

a = 4,235,000 ± 11,000
σ = 47,000 ± 8,000
c. v. = 1.1% ± 0.2%

Pipet D4

a = 4,223,000 ± 12,000
σ = 53,000 ± 9,000
c. v. = 1.3% ± 0.2%

Probable Error of the Difference Between Two Pipets

Probable error $(4{,}235 - 4{,}223) = \sqrt{11{,}000^2 + 12{,}000^2} = \sqrt{265{,}000{,}000} = 16{,}000$. The difference, 12,000, is less than its probable error, 16,000, and therefore it is not significant. "Unless a deviation is more than four times its probable error, there is no great reason for thinking it may not result from pure chance" (Gavett, G. I.: A First Course in Statistical Method, New York, McGraw Hill, 1925, p. 183).

* In this table, 431, etc., = number of cells counted in 80 small squares. n = 10. d = deviation from assumed average. a′ = assumed average = 423. a = average or arithmetic mean. d′ = deviation of average (a) from assumed average (a′).

TABLE 3.—*Total Red Counts: Cells per Cubic Millimeter (in Thousands); Original Data Table 13*

Technician	Mean	Probable Error	Standard Deviation	Probable Error	Coefficient of Variation, per Cent	Probable Error, per Cent	No. Drops from Pipet
C 1	4,639	±17	110	±12	2.3	±0.3	20
2	4,273	±15	99	±11	2.3	±0.3	20
3	4,476	±15	100	±11	2.2	±0.2	20
A 1	4,355	±26	170	±18	3.9	±0.4	20
2	4,286	±19	125	±14	2.9	±0.3	20
3	4,130	±14	90	±10	2.2	±0.2	20
4	4,038	±18	116	±13	2.9	±0.3	20
5	4,354	±13	83	± 9	1.9	±0.2	20
6	4,256	±10	74	± 7	1.7	±0.2	20
D 1	4,770	±18	82	±13	1.7	±0.3	10
2	4,679	±13	63	± 9	1.3	±0.2	12
3*	4,235	±11	47	± 8	1.1	±0.2	10
4*	4,223	±12	53	± 9	1.3	±0.2	10
F 1	3,928	− 5	24	− 4	0.6	−0.1	10
2	3,898	− 4	17	− 3	0.4	−0.1	10
3†	3,935	− 2	8	− 1	0.2	−0.03	10
4†.	3,931	− 2	7	− 1	0.2	−0.03	10

* D 3 and D 4 are two pipets from the same drop of blood.
† F 3 and F 4 are two pipets from the same drop of blood.

3 to 4 per cent is an index of fairly good technic when 20 drops are counted from the same pipet, but less than 3 per cent should be attained. Adequate shaking of the pipet and even distribution of the cells in the counting chambers are the necessary prerequisites.

2. The size of the difference between the means of cells counted from two pipets from the same drop of blood is influenced by the taking and the diluting of the blood as well as by the distribution of the cells in the counting chambers. The means will approach each other as the technic becomes more accurate, and the difference should never be more than three times its probable error. The definiteness of this method, in which the technician checks himself, is to be preferred to one in which a second person counts from the same drop. It also excludes any consideration of the time of day or of physiologic variations between practice periods if counts are made on different days.

Method.—Total counts were made with United States certified pipets and counting chambers on drops of blood from the finger tip. Hayem's fluid was the diluent. Two drops were counted from each pipet, or 160 small squares in all. Most of the data were obtained from women at half hour or hour intervals during eight hour periods on different days between the menses. All were in good health, although both the blood counts and hemoglobin determinations were low when compared with the normal standards. The investigation was purposely limited to a few people, because the aim was to study the daily variations of a small number of persons rather than scattered ones on many.

Observations.—Variations in total counts from 8 a. m. through 3 p. m. were as follows (table 4, chart 1):

4	series	16 counts	active (1, 2, 3, 10)
10	series	8 counts	active (4-9, 11-14)
1	series	16 counts	inactive 20
7	series	8 counts	inactive (15-19, 21, 22)
22	series	total	

Results.—Other data that had been accumulated earlier in the study were discarded because the errors were too large. All data, however, led to the conclusion that the red blood corpuscles remain almost constant in number during the day, and that the coefficient of variation for the day corresponds closely to the value previously obtained by the technician for the cells within the pipet. The accuracy of the technician should therefore always be known before conclusions are drawn concerning variations in total counts.

No difference is apparent between moderately active days and inactive ones for there is as much difference between two days of activity or two days of rest for the same person as between one of activity

and one of rest. Activity has meant in these cases counting, writing and typewriting, and inactivity, rest in bed. Table 4 and chart 1 show how closely these days resemble each other. Although afternoon

TABLE 4.—*Total Red Blood Cell Counts (in Thousands)*

	Technician	Subject	Date	Mean	Probable Error	Standard Deviation	Probable Error	Coefficient of Variation, per Cent	Probable Error, per Cent	Number
			8 a.m. Through 3 p.m. Active (1-14). Inactive (15-22). Original Data Table 11							
1	A	A	2/16/29	3,953	±19	109	±13	2.8	±0.3	16
2			2/17/29	4,005	±21	120	±15	3.0	±0.4	16
3			2/22/29	4,128	±24	137	±17	3.3	±0.4	16
4	D	B	7/27/29	4,281	±17	66	±12	1.5	±0.3	8
5			8/ 6/29	4,278	±10	38	± 7	0.9	±0.2	8
6	D	D	12/ 1/29	4,131	±14	54	±10	1.3	±0.2	8
7			11/ 3/29	4,364	± 5	21	± 4	0.5	±0.1	8
8	F	D	5/11/30	4,243	± 5	21	± 4	0.5	±0.1	8
9			5/16/30	4,230	± 4	15	± 3	0.4	±0.1	8
10	C	E	2/16/29	4,596	±17	99	±12	2.2	±0.3	16
11	F	G	2/16/30	4,603	±21	81	±15	1.8	±0.3	8
12			3/ 2/30	4,510	±16	62	±11	1.4	±0.3	8
13			3/ 9/30	4,405	±15	57	±10	1.3	±0.2	8
14			5/11/30	4,543	±11	41	± 7	0.9	±0.2	8
15	A	B	5/21/29	4,380	±14	53	±10	1.2	±0.2	8
16			5/27/29	4,491	±22	84	±15	1.9	±0.3	8
17	D	B	7/22/29	4,295	±23	90	±16	2.1	±0.4	8
18			7/28/29	4,255	±16	60	±11	1.4	±0.3	8
19			8/ 1/29	4,248	± 7	28	± 5	0.7	±0.1	8
20	A	E	5/ 5/29	4,213	±15	84	±10	2.0	±0.2	16
21			6/ 4/29	4,123	±20	76	±14	1.8	±0.3	8
22			6/ 5/29	4,175	±24	94	±17	2.3	±0.4	8
			4 p.m. Through 11 p.m. Active (27-32, 34-37). Inactive (23-26, 33)							
23	D	B	7/23/29	4,236	±17	66	±12	1.6	±0.3	8
24			7/26/29	4,205	±13	49	± 9	1.2	±0.2	8
25			7/31/29	4,223	± 4	17	± 3	0.4	±0.1	8
26			8/ 5/29	4,258	± 7	26	± 5	0.6	±0.1	8
27	F	B	5/ 3/30	4,100	± 4	17	± 3	0.4	±0.1	8
28			5/ 7/30	4,236	± 5	18	± 3	0.4	±0.1	8
29	D	D	10/31/29	4,131	± 4	15	± 3	0.4	±0.1	8
30			11/21/29	4,145	±19	73	±13	1.8	±0.3	8
31	F	D	5/ 7/30	4,034	±14	55	±10	1.4	±0.3	8
32			5/15/30	4,236	± 5	18	± 3	0.4	±0.1	8
33	B	E	6/16/29	3,745	±35	133	±24	3.5	±0.6	8
34	F	G	2/13/30	4,448	±14	54	±10	1.2	±0.2	8
35			4/ 6/30	4,195	± 5	19	± 3	0.5	±0.1	8
36			5/ 3/30	4,698	± 7	28	± 5	0.6	±0.1	8
37			5/ 4/30	4,521	±12	17	± 9	1.0	±0.2	8
			12 m. Through 7 a.m. Active (38). Inactive (39-41)							
38	A	A	2/24/29	3,860	±20	113	±14	2.9	±0.4	16
39	D	B	7/30/29	4,245	±10	40	± 7	0.9	±0.2	8
40			8/ 3/29	4,375	± 9	35	± 6	0.8	±0.1	8
41			8/ 4/29	4,283	± 8	31	± 7	0.7	±0.1	8

depressions appear in the composite curves for the active and inactive days taken separately and together, the decrease in the number of cells is so slight and the amount of data so small that the differences between the means for the morning and afternoon counts were found to be insignificant according to their probable errors.

The differences between the morning and afternoon counts were as follows:

8 a. m. through 11 a. m.
n = 44 11 series (1-7, 10-13)
a = 4,327,000 ± 47,000
12 m. through 3 p. m.
a = 4,261,000 ± 49,000
difference = 66,000 ± 68,000

8 a. m. through 11 a. m.
n = 76 19 series (1-7, 10-13, 15-22)
a = 4,312,000 ± 37,000
12 m. through 3 p. m.
a = 4,261,000 ± 37,000
difference = 51,000 ± 52,000

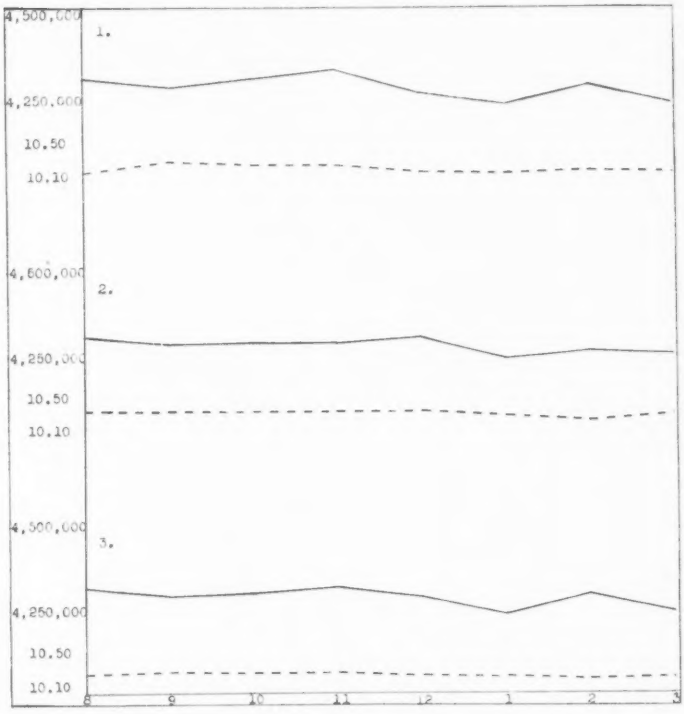

Chart 1.—Total erythrocyte counts and hemoglobin determinations; 8 a. m. through 3 p. m. The continuous line indicates the curve for the total erythrocytes; the broken line, that for the hemoglobin, in grams per hundred cubic centimeters. Curve 1: Erythrocytes composite curve, eleven series, active (1-7, 10-13) table 11. Hemoglobin, composite curve, eight series, active (1-8) table 12. Curve 2: Erythrocytes, composite curve, eight series, inactive (15-22) table 11. Hemoglobin, composite curve, five series inactive (9-13) table 12. Curve 3: Erythrocytes, composite curve, nineteen series (1-7, 10-13, 15-22). Hemoglobin, composite curve, thirteen series (1-13).

In six series no food was taken after breakfast (series 10, 15, 16, 20, 21, 22), and in the rest lunch was eaten between 12 and 2 o'clock. The average range (i. e., the difference between the highest and lowest items) for this period of the day for nineteen series (1-11, 15-22) is 251,000 ± 18,000, the maximum being 491,000 and the minimum, 60,000. These figures, which indicate the range of the counts, must also be interpreted according to the accuracy of the technic.

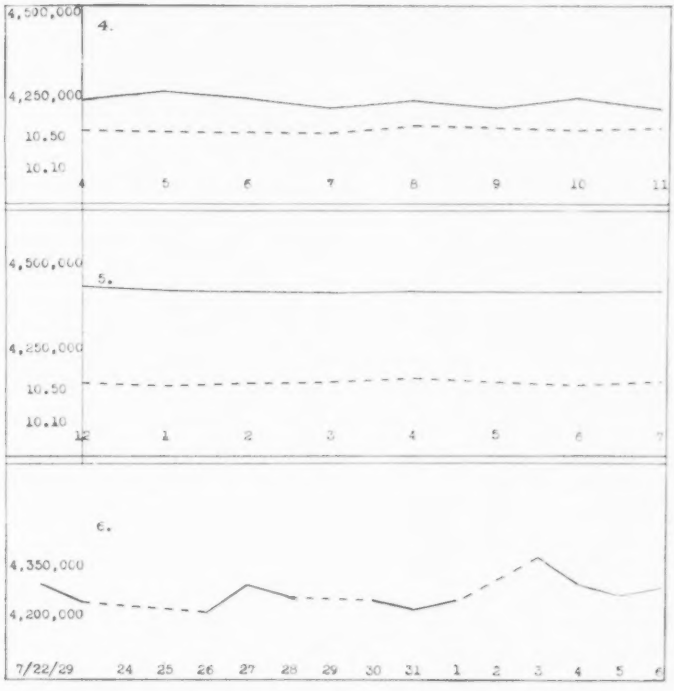

Chart 2.—Total erythrocyte counts and hemoglobin determinations; 4 p. m. through 11 p. m. and 12 m. through 7 a. m. Total erythrocyte counts, twelve eight hour counts over a sixteen day period. The continuous line indicates the curve for the total erythrocytes; the broken line, that for the hemoglobin, in grams per hundred cubic centimeters. Curve 4: Erythrocytes, composite curve, fifteen series (23-37) table 11. Hemoglobin, composite curve, five series (14-18) table 12. Curve 5: Erythrocytes, composite curve, four series (38-41) table 11. Hemoglobin, composite curve, seven series (19-25) table 12. Curve 6: Twelve eight hour erythrocyte counts in a sixteen day period. Each point is the average for the day, table 5. The broken line in the curve indicates the omission of counts.

Observations.—Variations in total counts from 4 p. m. through 11 p. m. (table 4, chart 2) were as follows:

10 series 8 counts active (27-32, 34-37)
5 series 8 counts inactive (23-26, 33)

15 series total

Results.—The data for this series of counts lead to the same conclusions as those just described for the 8 a. m. through 3 p. m. series. There were no fluctuations evident which were outside those that can be ascribed to technic. The depression in the afternoon which is seen in the curves for the day counts (8 a. m. and through 3 p. m.), but which cannot be proved as significant, seems to be continued in the evening as indicated by the lower values for these determinations. If the means for the 8 a. m. through 3 p. m. and the 4 p. m. through 11 p. m. counts for subjects, B, D and G are compared, singly and together, it is seen that in each case the one for the evening series is less than that for the day.

The differences between the day and evening counts were as follows:

Subject	8 a. m.–3 p.m.		4 p. m.–11 p. m.		Difference
B	(7 series)	4,318,000	(6 series)	4,210,000	108,000
D	(4 series)	4,242,000	(4 series)	4,137,000	105,000
G	(4 series)	4,515,000	(4 series)	4,466,000	49,000
B, D, G	(15 series)	4,351,000	(14 series)	4,264,000	87,000 ± 40,000

As the difference, 87,000, is only a little over two times its probable error, 40,000, there is, again, no proof statistically that the decrease toward evening is real. However, the patterns of the composite curves (charts 1 and 2) show a slight downward trend in the latter part of the day, and with more data and still more accurate technic this may prove to be significant.

Observations.—Variations in total counts from 12 m. through 7 a. m. were as follows (table 4, chart 2):

1 series 8 counts active (38)
3 series 8 counts inactive (39-41)

4 series total

Results.—Although the number of series is limited, the data indicate again the constancy of the red blood cell count during a limited period of time. There are no variations outside the limit of error for the technic and no characteristic pattern. It is probable that the increase and decrease of cells during the twenty-four hour period are so gradual that the differences appear only between counts for days, as will be noted in the discussion of the longer series.

VARIATIONS DURING LONGER PERIODS

Although the fluctuations during eight hour periods are so slight that they cannot be proved significant statistically with the amount of data on hand, the variations from day to day may be real. One day, Aug. 3, 1929, showing an actual difference (i. e., above the limit of error) from the one preceding (Aug. 1, 1929) and the one following (Aug. 4, 1929) is seen in the twelve day series in table 5. The test for the significance of the difference between days' counts is the same as that used for the difference between two pipets. Study on this particular phase of the problem is still in progress (Smith,[3] 1930). It is probable that these fluctuations and the wider distribution of the

TABLE 5.—*Total Red Counts on Subject B (Twelve Series in Sixteen Day Period)*

Date	Time	Condition	Total Red Mean in Thousands	Probable Error	Difference ÷ Probable Error
7/22/29	8-3	Inactive	4,295	±23	
7/23/29	4-11	Inactive	4,236	±17	2.1
7/26/29	4-11	Inactive	4,205	±13	1.4
7/27/29	8-3	Active	4,281	±17	3.6
7/28/29	8-3	Inactive	4,255	±16	1.1
7/30/29	12-7	Inactive	4,245	±10	0.5
7/31/29	4-11	Inactive	4,223	± 4	2.6
8/ 1/29	8-4	Inactive	4,248	± 7	3.1
8/ 3/29	12-7	Inactive	4,375	± 9	11.1
8/ 4/29	12-7	Inactive	4,283	± 8	7.7
8/ 5/29	4-11	Inactive	4,258	± 7	2.4
8/ 6/29	8-4	Active	4,278	±10	1.6

cells as indicated by the larger standard deviations for most of the longer series are related (table 6). Nevertheless, it is interesting to see how closely the averages for the same person compare for different times of the year. The February, 1929, average for A (3,989,000) is significantly different from the summer average of 1928 (4,131,000), and the one of February-March, 1929 (4,123,000), but the difference between the latter two is not significant according to its probable error. Too much weight cannot be placed on the average, 3,989,000 (February, 1929), because it represents counts for only four days. The twenty-two day count taken later in February and March of the same year is interesting, as the subject was receiving spleen-marrow medication. The

3. Smith, C.: Normal Variations in Red-Blood-Cell Counts Over Long Periods of Time, Anat. Rec. **45**:278, 1930.

means for B for 1928, 1929 and 1930 are so nearly alike that their differences are about equal to their probable errors, The data for both A and B give no evidence of marked seasonal variation.

HEMOGLOBIN DETERMINATIONS

Technic.—As with the counting of the erythrocytes, the problem in estimating the hemoglobin content of the blood is the acquisition of an accurate technic. Although Van Slyke's method is acknowledged to be the most accurate, the Duboscq colorimeter with the hemoglobin attachment was chosen as the apparatus with which determinations could be made as quickly and as simply as possible.

TABLE 6.—*Total Red Blood Cell Counts Over Longer Periods (in Thousands)*

Subject	Date	Season	Mean	Probable Error	Standard Deviation	Probable Error	Coefficient of Variation, per Cent	Probable Error, per Cent	Number
A	1928	Summer	4,131	±12	240	± 9	5.8	±0.2	173
	1929	February	3,989	±13	160	±10	4.0	±0.2	64
	1929	February-March	4,123	±17	120	±12	2.9	±0.3	22
B	1928	Summer	4,308	±20	285	±14	6.6	±0.3	96
	1929	Summer	4,288	± 6	94	± 4	2.2	±0.1	116
	1930	January-February	4,267	±27	279	±19	6.5	±0.4	51
D	1929	Autumn	4,256	±35	467	±25	11.0	±0.6	80
E	1929	Spring	4,241	±27	295	±19	7.0	±0.5	56
G	1930	Spring	4,496	±38	398	±27	8.9	±0.6	51
H	1929	Autumn	4,407	±28	311	±19	7.1	±0.4	58

A n* = 173 determinations in 19 days
n = 64 determinations in 4 days
B n = 96 determinations in 7 days
n = 116 determinations in 15 days

* In all other series n also indicates the number of days counted.

The errors inherent in the method are different from those in total counting. The measuring and the dilution of the blood can be made easily. The wrong angle of the mirror, an inadequate source of light and fatigue of the observer may contribute to the inaccuracy of the results. Osgood [4] (1926) found errors as large as 12 per cent in hemoglobin estimations with the Bausch and Lomb Newcomer Hemoglobinometer. As many determinations recorded in this paper were made at night, most values were obtained with light through an 8 inch (20.32 cm.) Corning daylight disk, although some were made with northern light and some with a daylight bulb. Comparative figures were obtained on the same blood before this procedure was adopted, and the results were found to be practically the same. In series in which determina-

4. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards, Arch. Int. Med. **37**:685 (May) 1926.

tions were made every half hour, the readings were taken at twenty, twenty-five and twenty-eight minutes after dilution, and in those made every hour, thirty, thirty-five and thirty-eight minutes later. The number of grams given for each hour is the mean of at least nine readings. The yellow filter used throughout this work gave a value of about 3.25 Gm. less than that obtained with the Van Slyke apparatus for the same blood.

The same test for the accuracy of the method was used as for the total counts. Twenty readings were made from the same pipet, and a coefficient of variation less than 1 per cent with a probable error less than 0.1 per cent could be obtained. Two pipets filled from the same drop of blood were found to have means the difference of which was less than two times its probable error. Despite this precision and care in the uniform lighting of the mirror, variations have appeared in the series of daily determinations over a long period of time which are hard to understand.

Observations.—Variations in hemoglobin determinations from 8 a. m. through 3 p. m. were as follows (table 7, chart 1):

8 series 16-20 determinations active (1-8)
5 series 8-16 determinations inactive (9-13)

Results.—The hemoglobin determinations fluctuate very little during the day, and the slight changes that appear lie within the limit of error for the method. As with the curves for the total counts, a slight depression is seen in the afternoon in the composite curve (chart 1) plotted from data for both the active and the inactive days. The means and their probable errors were computed for the morning and afternoon figures with the following results:

8 a. m. through 11 a. m.	*12 m. through 3 p. m.*
n = 49 (series 1-13)	n = 52 (series 1-13)
a = 10.279 ± 0.041	a = 10.217 ± 0.043
difference = 0.062 ± 0.059	

As the difference is almost equal to its probable error, there is no reason from these data to believe that the decrease in value in hemoglobin is a real diminution.

Observations.—Variations in hemoglobin determinations from 4 p. m. through 11 p. m. and 12 m. through 7 a. m. were as follows (table 7, chart 1):

5 series 4-11 inactive (14-18)
7 series 12-7 inactive (19-25)

Results.—From both chart 1 and table 7 it is apparent that the hemoglobin values do not change significantly within short periods of time. When the determinations for subjects B and E are compared for the different times of day, it would seem that those for the afternoon and evening were higher than those for the daytime. However, if the differences between the means and their probable errors are computed, it is found that they are not real.

TABLE 7.—*Hemoglobin Determinations (Grams per Hundred Cubic Centimeters of Blood)*

		8 a.m. Through 3 p.m.		Active (1-8)	Inactive (9-13)	Original Data Table 12			
	Subject	Date	Mean	Probable Error	Standard Deviation	Probable Error	Coefficient of Variation, per Cent	Probable Error, per Cent	Number
1	A	8/ 2/28	10.191	±0.012	0.073	±0.008	0.72	±0.081	19
2		8/ 3/28	10.215	±0.012	0.075	±0.009	0.73	±0.085	18
3		2/16/29	10.086	±0.02	0.113	±0.014	1.12	±0.137	16
4		2/17/29	10.100	±0.013	0.075	±0.009	0.74	±0.091	16
5		2/22/29	10.220	±0.005	0.030	±0.004	0.29	±0.036	16
6	B	8/10/28	10.180	±0.017	0.096	±0.012	0.94	±0.115	16
7		8/14/28	10.518	±0.028	0.164	±0.020	1.56	±0.191	16
8		8/15/28	10.123	±0.008	0.044	±0.005	0.43	±0.053	16
9		5/27/29	10.186	±0.013	0.052	±0.009	0.51	±0.093	8
10		8/ 1/29	10.700	.....	.....	.....	....	.....	8
11	E	5/ 5/29	10.445	±0.020	0.113	±0.014	1.08	±0.132	16
12		6/ 4/29	10.141	±0.019	0.072	±0.013	0.71	±0.129	8
13		6/ 5/29	10.138	±0.010	0.039	±0.007	0.38	±0.069	8
		4 p.m. Through 11 p.m.							
14	B	7/31/29	10.699	±0.009	0.033	±0.006	0.31	±0.056	8
15		8/ 5/29	10.535	±0.009	0.035	±0.006	0.33	±0.060	8
16	E	6/15/29	10.528	±0.029	0.110	±0.020	1.04	±0.190	8
17		6/16/29	10.631	±0.028	0.109	±0.020	1.03	±0.188	8
18		6/17/29	10.534	±0.012	0.047	±0.009	0.45	±0.082	8
		12 m. Through 7 a.m.							
19	B	7/30/29	10.773	±0.027	0.107	±0.019	0.99	—0.180	8
20		8/ 3/29	10.700	.....	.....	.....	....	.....	8
21		8/ 4/29	10.715	±0.007	0.026	±0.005	0.24	±0.044	8
22	E	6/19/29	10.559	±0.022	0.083	±0.015	0.79	±0.144	8
23		6/20/29	10.455	±0.007	0.026	±0.005	0.25	±0.045	8
24		6/21/29	10.333	±0.008	0.029	±0.005	0.28	±0.051	8
25		6/23/29	10.453	±0.022	0.084	±0.015	0.80	±0.146	8

The differences between day, evening and night hemoglobin determinations in subjects B and E were as follows:

1.	2.	3.
8 a. m. through 3 p. m.	*4 p. m. through 11 p. m.*	*12 m. through 7 a. m.*
10.304 ± 0.053	10.585 ± 0.231	10.569 ± 0.043

Difference between 1 and 2 = 0.281 ± 0.237
Difference between 2 and 3 = 0.016 ± 0.235.

VARIATIONS DURING LONGER PERIODS

The changes in the hemoglobin values over longer periods of time may be real, as are those of the total red counts, but as determined with the Duboscq colorimeter they do not always parallel those of the

cells. These are the variations mentioned previously which are difficult to understand if it is assumed, as many do, that the hemoglobin values vary directly with the total red counts. Although the total counts for subject A for the summer of 1928 and February-March, 1929, are not significantly different, the hemoglobin determination for the same periods are (table 8). A real difference is also found between the hemoglobin values for 1928-1929 and 1929-1930 for subject B, whose total counts were not found to vary from one year to another.

TABLE 8.—*Hemoglobin Determinations Over Longer Periods (Grams per Hundred Cubic Centimeters of Blood)*

Subject	Date	Season	Mean	Probable Error	Standard Deviation	Probable Error	Coefficient of Variation, per Cent	Probable Error, per Cent	Number
A	1928	Summer	10.41	0.023	0.36	0.017	3.4	0.16	108
	1929	February-March	10.21	0.03	0.22	0.02	2.2	0.23	22
B	1928	Summer	10.40	0.035	0.39	0.025	3.9	0.25	56
	1929	Summer	10.62	0.018	0.20	0.013	1.9	0.12	56
	1930	January-February	10.346	0.059	0.615	0.041	5.94	0.401	50
D	1929	Autumn	10.21	0.045	0.581	0.032	5.69	0.313	71
E	1929	Spring	10.41	0.012	0.17	0.009	1.6	0.08	87
H	1929	Autumn	10.204	0.052	0.368	0.037	5.57	0.362	54

A n* = 108 determinations in 11 days

B n = 56 determinations in 4 days in 1928
n = 56 determinations in 7 days in 1929

E n = 87 determinations in 10 days

* In all other series n also indicates the number of days counted.

The differences between the means and their probable errors were as follows:

A Difference 1928-1929 = 0.20 ± 0.037
B Difference 1929-1930 = 0.054 ± 0.069
B Difference 1929-1930 = 0.274 ± 0.062.
B Difference 1928-1929 = 0.220 ± 0.039

COMMENT

Total Red Counts.—As in the study of the leukocytes, much of the previous work on red blood corpuscles has been on the determination of a normal average derived from values for many persons rather than from daily variations in individuals. Of those who have worked on the latter phase of the erythrocyte problem, some believe in a constant number and some in a widely varying one. Table 9 reviews in a brief way some of the evidence for and against a fluctuating red blood cell count. According to these investigators, there may be no

real variations in a day (Lyon,[5] Nonnenbruch,[6] and Rud[7]), small variations (Hayem,[8] Reinert,[9] Ward,[10] Craandyk,[11] Komocki,[12] Leake, Kohl and Stebbins,[13] and Stebbins and Leake[14]) or large variations (Schwinge,[15] Bing,[16] Bierring,[17] Lasch and Billich,[18] Doan and Zerfas[19] and Sabin[20]).

A sharp line cannot be drawn in this previous work between "no real variations" in a day and "small variations" for at least two reasons. The first is that the figures represent averages for different numbers of hours, and the second that the error involved in the technic is not known

5. Lyon, J. F.: Blutkörperzählungen bei traumisch Anämie, Virchows Arch. f. path. Anat. **84**:207, 1881.

6. Nonnenbruch, W.: Ueber extrarenale Ödemgenese und Vorkommen von konzentrierten Blut bei hydropischen Nierenkranken, Deutsches Arch. f. klin. Med. **136**:170, 1921.

7. Rud, E. J.: Le nombre des globules rouges chez les sujets normaux et leurs variations dans les diverses conditions physiologiques: I. L'influence de l'âge et du sexe sur le nombre des globules rouges, Acta med. scandinav. **57**:142, 1922-1923; II. Les variations du nombre des globules rouges dans les diverses conditions physiologiques, ibid. **57**:325, 1922-1923.

8. Hayem, G.: Des caractères anatomiques du sang dans les anémies, Comp. rend. Acad. d sc. **83**:230, 1876; Du sang et de ses altérations anatomiques, Paris, Masson & Cie, 1889.

9. Reinert, E.: Die Zählung der Blutkörperchen und deren Bedeutung für Diagnose und Therapie, Leipzig, F. C. W. Vogel, 1891.

10. Ward, H. C.: The Hourly Variations in the Quantity of Haemoglobin and in the Number of the Corpuscles in Human Blood, Am. J. Physiol. **11**:394, 1904.

11. Craandyk, M. M.: Beitrag zum morphologischen Blutbilde im Hochgebirge, Folia haemat. **23**:11, 1918-1919.

12. Komocki, W.: Einige Bemerkungen zur Frage der Zahl der Erythrozyten im Menschenblute, Wien. klin. Wchnschr. **40**:1057, 1927.

13. Leake, C.; Kohl, M., and Stebbins, G.: Diurnal Variations in the Blood Specific Gravity and Erythrocyte Count in Healthy Human Adults, Am. J. Physiol. **81**:493, 1927.

14. Stebbins, G., and Leake, C. D.: Specific Gravity of Blood, Am. J. Physiol. **80**:639, 1927.

15. Schwinge, W.: Untersuchung über das Hämoglobingehalt und die Zahl der rothen und weissen Blutkörperchen, Arch. f. d. ges. Physiol. **73**:299, 1898.

16. Bing, H. I.: Antallet af røde blodlegemer i de forskellige åldre og under forskellige forhold, Ugesk. f. læger. **81**:1483, 1919.

17. Bierring, K.: Svingninger i erythrocyttallet hos normale mennesker, Ugesk. f. læger. **82**:1445, 1920.

18. Lasch, C. H., and Billich, H. U.: Die täglichen Schwankungen der Erythrocytenzahlen, zugleich ein Beitrag zur Frage der Blutwasserbestimmung, Ztschr. f. d. ges. exper. Med. **48**:651, 1925-1926.

19. Doan, C. A., and Zerfas, L. G.: The Rhythmic Range of the White Blood Cells in Human, Pathological Leucopenic and Leucocytic States, with a Study of 32 Human Bone Marrows, J. Exper. Med. **46**:511, 1927.

20. Sabin, F. R.: Bone Marrow, Physiol. Rev. **8**:226, 1928.

TABLE 9.—*Variations in Red Blood Cells During the Day and from Day to Day*

Author	Date	Coefficient of Variation, %	Variations in a Day		Variations Between Days		Comment
			Small	Large	Small	Large	
Hayem [8]	1876 1889	....	Very slight beyond error	.....	.....	.....	More in young
Lyon [5]	1881	....	Slight within error	.....	Real	Lyon "fairly" large	16 days, 4 observations each day (1.7% coefficient of variation) (Rud, probably not real)
Reinecke, W.: Dissert., Halle	1889	....	.....	.....	.....	Large	12 days, 3 times a day
Reinert [9]	1891	2.97	Real	.....	Real	.....	7 days, every 2 hours (almost 6% coefficient of variation during 15 to 21 hour periods)
Schwinge [15]	1898	....	.....	Coefficient of variation, 5%	Close relation of means	.....	2 series, 2 and 3 days; 4 series every 2 hours 8 a.m. to 8 p.m.; coefficient of variation about 5%
Ward [10]	1904	....	Vary through range 5%	.....	.....	.....	9 days 4 persons average difference between a.m. and p.m. 250,000
Bürker, K.: München. med. Wchnschr. **59**: 89, 1912	1912	1.8	.....	.....	No essential difference	.....	7 consecutive days
Bing [16]	1919	2.3	.....	Range: 6-700,000 in a day	.....	.....	
Craandyk [11]	1918-1919	3.1 3.4	Vary 50,000 to 470,000	.....	Agrees with Bürker	.....	4 men, 7 women, 2 counts early and late morning, 7 increase, 3 decrease
Bierring [17]	1920	3.2	.....	500,000 outside error	.....	Large 1,000,000	Largest absolute difference, 2.4 million, largest daily variation, 1.4 million; variations characteristic of individual
Nonnenbruch [6]	1921	....	Constant	.....	.....	.....	
Rud [7]	1922-1923	2.0	No real	.....	Rare and small	.....	5 series, 2-6 times daily; 4 series, 5-7 days each; 4 series weekly, 3-4 months; 3 series, 6-7 determinations, 6 months
Komocki [2, 12]	1924 1927	...	..... Small	.....	Small	.....	Difference between successive counts of same individual less than 200,000
Mills, E. S.: Arch. Int. Med. **35**: 760 (June) 1925	1925	....	.....	.....	.....	.....	16 cases of anemia, every 2 hours, 8 a.m. through 6 p.m., average variation 250,000
Lasch and Billich [18]	1925-1926	2.6	.....	Large	.....	.....	3 times in 24 hours, average difference 4-600,000; smallest 130,000, may be 900,000 in 24 hours
Doan and Zerfas [19]	1927	....	.....	Large	.....	.....	3 hour counts, 15 minute intervals, difference of 1,000,000
Stebbins and Leake [14]	1927	....	.....	.....	.....	.....	Coefficient for day 1.6%
Leake, Kohl and Stebbins [13]	1927	....	Small	.....	.....	.....	Average diurnal variation for women, 310,000; for men, 345,000
Sabin [20]	1928	....	.....	Large	.....	.....	Range of 1,000,000

in each case. When the latter is not given, it is impossible to evaluate the data except by comparison with data presented in this paper. It has been shown that the average range for the 8 a. m.-3 p. m. counts for 19 series is 251,000 ± 18,000, with a maximum of 490,000, and the coefficient of variation for over half the counts is seen to be less than 2 per cent (table 4). Therefore, figures that are given as indicating small variations may well be within the limit of error of fairly accurate technic (Ward,[10] Craandyk,[11] Komocki,[12] Leake, Kohl and Stebbins [13] and Stebbins and Leake [14]). There is no way to judge the validity of the conclusions of Hayem,[8] and those of Reinert [9] appear to be according to his data.

The large variations that are cited are outside the limit of error if that has been determined for the method and found to be small. Bing,[16] Bierring [17] and Lasch and Billich [18] have given values for the error involved in the method (2.3, 3.2 and 2.6 per cent, respectively, table 9). However, Bierring [17] eliminated one large variation from his result as due to technic, previously noted by Rud,[7] and therefore lessened the worth of the coefficient of variation quoted by him. Although the range of cells in twenty-four hours noted by Lasch and Billich [18] is larger, as might be expected, than that given for eight hour periods in this paper, it is also greater than the differences usually found between daily counts over longer periods of time (table 5 and unpublished data). The appraisal of the figures given by Bing [16] and Lasch and Billich [18] is also rendered more difficult because they found differences in the cell content of the blood from different parts of the body, which is not in accordance with other work on this phase of the erythrocyte problem (Reichel and Monasterio,[21] 1929). Schwinge,[15] Doan and Zerfas [19] and Sabin [20] gave no information as to the error involved in their technic. Sabin [20] stated her conclusions concerning the fluctuations in total red cell count as follows: "Sabin . . . and Doan and Zerfas . . . have shown that the delivery of red cells from the marrow is rhythmic with a range of about 1,000,000 cells between the high and low counts each day; as far as their observations have gone the rhythm does not follow that of the white cells, with the marked rise in the afternoon, but rather the high points come both morning and afternoon."

The data presented in this paper support the conclusions that within short periods of time, certainly the eight hour periods investigated, the total red blood cell count is practically constant, and that any fluctuations present are within the limit of error of the method. In order to

21. Reichel, J., and Monasterio, G.: Beiträge zur Frage der numerischen Verteilung der Erythrocyten und Leucocyten an der Peripherie, Klin. Wchnschr. **8**:1712, 1929.

evaluate correctly normal changes in blood cell content or those due to experimental procedure, the accuracy of the technician must be definitely known. The parallelism of the coefficients of variations for cells within pipets with those for day counts by the same technician is striking (tables 3 and 4). Furthermore, increased efficiency on the part of the technician always resulted in a decreased value for the coefficient of variation for the periods counted.

The depression of the curve for red cells in the afternoon has been reported by Reinert,[9] Ward [10] and Rud.[7] Reinert [9] found a real difference between 12 and 2 o'clock, and Ward,[10] following Reinert [9] in method, found an average decrease of 250,000 cells in the late afternoon counts of 4 men in a nine day series. Ward [10] also made 150 isolated morning and 185 afternoon counts on different persons and obtained an average difference of 300,000 cells. Rud [7] described diminutions at the end of the day which do not pass beyond the limits of error for the method, but he added that on the other hand they come with such regularity that one is not able to refrain from thinking that they are not fortuitous. The results obtained in this study confirm Rud's point of view. Although the morning and afternoon and the day and evening counts show a decrease in the last part of the day, it cannot be proved statistically with the amount of data on hand.

The drop after meals reported by Hayem,[8] Reinert [9] and Leake, Kohl and Stebbins [13] is found uncertain by Lyon,[5] Bing [16] and Rud.[7] Reinert [9] quoted Vierordt as believing that the decrease is due to the dilution of the blood after the intake of water. However, Bing [16] found no decrease after starving persons for twelve hours and then having them drink a liter of water, and Rud [7] found no clear evidence that the adsorption of water played any rôle in the variations of red cells. From the data collected in this study there is no evidence that the intake of food or water influences the total red blood cell count. Breakfast was always eaten just before the first count in the day series and lunch usually at 1 or 1:30 p. m.; in the 4 to 11 p. m. series dinner came at 6:30 p. m., and during the night no food was taken. In the cases in which nothing was eaten after breakfast, there was no increase in the number of cells during the day, although fasting is said to result in larger counts (Hayem,[8] Duperie after Reinert [9]). Conclusions cannot be drawn, however, concerning the effect of fasting on the red cell count as the amount of data is too small and the time of fasting too short.

The curve for the numbers of red cells in the peripheral blood during the day and night is in no way correlated with that for the leukocytes. The marked fluctuations and the increase in the afternoon which are characteristic of the curves of white cells of fairly active

people (Sabin, Cunningham, Doan and Kindwall,[22] 1925; Smith and McDowell,[23] 1929) are not seen in red cell curves made at the same time (unpublished data). This has been noted by Sabin, Cunningham, Doan and Kindwall[22] and by Doan and Zerfas.[19] Glaser[24] (1928) expressed the belief, on the contrary, that the red and white counts show analogous changes in his study of Widal's hemoclastic crisis.

Significant changes have been found to be present between counts for days in a long series of successive daily counts (table 5 and Smith[3]). These variations will not necessarily show if the period is short, e. g., the seven day series of Bürker[25] and Rud,[7] who found no essential differences. In the longer series of Rud[7] the counts are too scattered to give accurate information, but he concluded from them that the real variations present are relatively rare and small. One must therefore believe with Rous[26] in "the existence under ordinary circumstances of a delicately balanced coordination between the rates of cell formation and cell destruction," for the variations of red cells during short periods of time are so small as to be within the limit of error of the method and appear as real deviations only in longer series of counts.

Hemoglobin Determinations.—Variations in hemoglobin determinations are similar and parallel to those of the total red counts that have been described by Ward,[10] Doan and Sabin[27] (1927), Doan and Zerfas[19] and Ponder and Millar.[28] Doan and Zerfas[19] and Rud[7] stated that the changes are smaller than those of the total counts, and Rud added, less frequent. Doan and Sabin,[27] however, pointed out in their work on experimental tuberculosis that the increases in hemoglobin may precede those in total cells.

Large diurnal variations (in hemoglobin estimations) have been found more frequently than small ones by previous investigators (table

22. Sabin, F. R.; Cunningham, R. S.; Doan, C. A., and Kindwall, J. A.: The Normal Rhythm of the White Blood Cells, Bull. Johns Hopkins Hosp. **37**:14, 1925.

23. Smith, C., and McDowell, A. M.: Normal Rhythm of White Blood Cells in Women, Arch. Int. Med. **43**:68 (Jan.) 1929.

24. Glaser, F.: Vegetatives Nervensystem und Blutzusammensetzung, Folia haemat. **35**:353, 1928.

25. Bürker, K.: Ueber Prüfung und Eichung des Sahlischen Hämometers und über Verbesserungen der Methoden der Erythrozytenzählung und Hämoglobinbestimmung, München. med. Wchnschr. **59**:89, 1912.

26. Rous, P.: Destruction of the Red Blood Corpuscles in Health and Disease, Physiol. Rev. **3**:75, 1923.

27. Doan, C. A., and Sabin, F. R.: Tuberculosis in the Bone Marrow, J. Exper. Med. **46**:315, 1927.

28. Ponder, E., and Millar, W. G.: The Measurement of the Diameters of Erythrocytes, Quart. J. Exper. Physiol. **19**:145, 1928.

10). Schwinge,[15] Ward[10] and Mills[29] gave 5 per cent as the size of the variations in a day, while Dreyer, Bazett and Pierce[30] and Rabinovitch[31] found variations of 10 per cent common. Even with one type of apparatus (i. e., the Van Slyke), the variations range from 5 to 10 per cent according to the investigator.

TABLE 10.—*Daily Variations in Hemoglobin Determinations*

Author	Date	Apparatus	Error in Method	Variations in Day	Variations from Day to Day
Reinert[9]	1891	.....	.....	Quotes Leichtenstern, highest at 12, lowest at 4	
Schwinge[15]	1898	Fleischel-Miescher	.....	5% variation 8 a.m. to 8 p.m.	
Ward[10]	1904	Fleischel	More open to error	Varies directly with red, about 5%	
Terhola, L.: Arch. f. Gynäk. **103**: 115, 1914	1914	Fleischel-Miescher; Sahli	16 duplicate counts, 0.37%; isolated, 26%, 16, 2.7%; isolated count, 1.9%		
Dreyer, Bazett and Pierce[30]	1920	Dubosecq	0.3% for readings	10% in day common, smallest between 5-7 p.m., greater variations in low hemoglobin values	
Rud[7]	1922-1923	Autenrieth-Königsberger	10 determinations, each the average of 5 readings; 1.7%; 1.8%	No real variations	Less frequent than reds, over longer periods within limits of error
Rabinovitch[31]	1923-1924	Van Slyke	.....	Average range, 20 people, 6 times a day, 12%; p.m. less than a.m.	
Mills[29].....	1925	Van Slyke; Dare	.....	16 cases of pernicious anemia; 4, anemia, every 2 hours, 8 a.m. to 8 p.m. variation 5.1% Van Slyke; 5.5% Dare	
Brandt, T.: Folia haemat. **32**: 177, 1926	1926	Sahli	1%		
Osgood[4]	1926	Bausch and Lomb Newcomer hemoglobinometer Osgood	12% error Maximum not over 2%		
Doan and Zerfas[19]...	1927	Dubosecq	.....	Varies about one-half that of cells and parallels changes in reds	
Ponder and Millar[28]..	1928	Palmer's colorimetric method	±1.5%	Follows red curves	

29. Mills, E. S.: Hourly Hemoglobin Variations in Anemias, Arch. Int. Med. **35**:760 (June) 1925.

30. Dreyer, G.; Bazett, H. C., and Pierce, H. F.: Diurnal Variations in the Hemoglobin Content of the Blood, Lancet **2**:588 (Sept. 18) 1920.

31. Rabinovitch, I. M.: Variations of the Percentage of Hemoglobin in Man During the Day, J. Lab. & Clin. Med. **9**:120, 1923-1924.

TABLE 11.—*Original Data: Red Blood Cell Counts (in Ten Thousands)*

	1	2	3	4	5	6	7	8	9	10	11	12
8 a.m.	417	406	399	437	433	418	437	422	425	440	451	460
8:30	400	432	437	...	...	...	...	...	...	458		
9	404	388	400	431	429	417	437	423	424	461	455	459
9:30	389	407	440	...	...	...	...	...	...	462		
10	398	400	406	429	434	413	433	424	424	466	476	457
10:30	415	360	417	...	...	...	....	...	...	467		
11	399	414	426	435	423	420	438	425	423	470	467	450
11:30	408	411	403	...	...	...	...	...	...	465		
12	384	404	408	426	427	412	439	429	424	445	462	446
12:30	394	394	414	...	...	...	...	...	...	468		
1	384	385	400	427	426	412	438	424	422	456	452	443
1:30	381	391	420	...	...	...	...	...	...	454		
2	387	399	425	426	423	401	436	422	420	469	464	447
2:30	385	401	398	...	...	...	...	...	...	454		
3	389	403	394	414	427	412	433	425	422	444	455	446
3:30	390	383	417	...	...	...	...	...	...	475		

	13	14	15	16	17	18	19	20	21	22
8 a.m.	453	458	435	462	434	431	428	437	403	414
8:30	...	...	...	...	...	...	...	417		
9	438	458	440	447	449	415	422	418	428	403
9:30	...	...	...	...	...	...	...	404		
10	435	457	439	453	425	425	427	422	415	420
10:30	...	...	...	...	...	...	...	432		
11	437	455	434	438	422	433	422	431	410	437
11:30	...	...	...	...	...	...	...	415		
12	439	457	441	444	431	430	425	433	415	422
12:30	...	...	...	...	...	...	...	415		
1	435	450	430	462	423	419	421	417	402	421
1:30	...	...	...	...	...	...	...	421		
2	443	446	436	444	433	429	429	418	414	412
2:30	...	...	...	...	...	...	...	413		
3	444	453	449	443	419	422	424	422	411	411
3:30	...	...	...	...	...	...	...	426		

	23	24	25	26	27	28	29	30	31	32	33	34
4 p.m.	435	416	421	426	407	424	415	416	410	424	368	446
5	430	426	425	432	409	424	414	414	408	427	387	436
6	413	423	422	426	411	427	413	420	410	424	368	451
7	419	417	424	424	409	425	412	419	394	425	364	436
8	419	427	423	425	412	424	411	419	397	422	375	450
9	428	425	420	426	409	421	415	418	402	422	366	444
10	422	415	420	424	411	422	414	414	403	421	404	448
11	423	415	423	423	412	422	411	396	403	424	364	447

	35	36	37
4 p.m.	418	472	463
5	420	472	453
6	419	473	451
7	418	472	449
8	419	469	448
9	423	465	447
10	417	466	452
11	422	469	454

	38	39	40	41
12 m.	413	433	438	430
12:30	387			
1 a. m.	396	423	443	434
1:30	401			
2	381	426	440	430
2:30	394			
3	372	422	440	428
3:30	368			
4	387	419	436	428
4:30	371			
5	382	421	433	428
5:30	389			
6	391	426	432	423
6:30	379			
7	386	426	438	425
7:30	379			

February, 1929
Subject A

400	437
432	424
437	410
379	410
====	420
404	413
377	411
420	410
415	400
416	417
404	410
401	422
427	411
409	

TABLE 12.—*Original Data: Hemoglobin Determinations (Grams per Hundred Cubic Centimeters)*

	1	2	3	4	5	6	7	8	9
8 a. m.	10.25	10.37	9.85	10.08	10.19	.....	.....	.....	10.31
8:30	10.37	10.37	9.91	10.19	10.25				
9	10.25	10.19	10.14	10.19	10.19	10.44	10.57	10.19	10.14
9:30	10.31	10.19	10.08	10.14	10.19	10.12	10.31	10.08	
10	10.25	10.37	10.25	10.08	10.25	10.19	10.37	10.19	10.19
10:30	10.19	10.19	10.14	10.08	10.25	10.14	10.37	10.08	
11	10.19	10.14	10.19	10.25	10.19	10.31	10.44	10.08	10.19
11:30	10.14	10.19	10.08	10.19	10.25	10.31	10.37	10.08	
12	10.19	10.19	10.02	10.14	10.25	10.08	10.37	10.08	10.19
12:30	10.14	10.25	10.19	10.08	10.19	10.14	10.50	10.02	
1	10.19	10.19	9.96	10.02	10.25	10.08	10.50	10.08	10.14
1:30	10.14	10.25	10.02	10.02	10.19	10.10	10.76	10.14	
2	10.08	10.14	10.14	10.02	10.25	10.16	10.50	10.08	10.14
2:30	10.25	10.25	10.02	10.08	10.19	10.25	10.96	10.25	
3	10.19	10.08	10.14	9.96	10.19	10.14	10.44	10.14	10.19
3:30	10.14	10.14	10.25	10.08	10.25	10.14	10.63	10.14	
4	10.14	10.25	.....	.....	.....	10.14	10.63	10.14	
4:30	10.14	10.19	.....	.....	.....	10.14	10.57	10.19	
5	10.08								

	10	11	12	13		14	15	16	17	18
8 a. m.	10.70	10.63	10.02	10.08	4 p. m.	10.63	10.50	10.63	10.63	10.57
8:30	.....	10.44								
9	10.70	10.57	10.19	10.08	5	10.70	10.57	10.57	10.50	10.50
9:30	.....	10.44								
10	10.70	10.44	10.19	10.14	6	10.70	10.50	10.50	10.63	10.50
10:30	.....	10.50								
11	10.70	10.50	10.19	10.14	7	10.76	10.50	10.44	10.50	10.50
11:30	.....	10.44								
12	10.70	10.50	10.19	10.14	8	10.70	10.57	10.76	10.57	10.50
12:30	.....	10.31								
1	10.70	10.31	10.19	10.19	9	10.70	10.57	10.44	10.76	10.57
1:30	.....	10.37								
2	10.70	10.31	10.02	10.14	10	10.70	10.50	10.44	10.63	10.63
2:30	.....	10.37								
3	10.70	10.31	10.14	10.19	11	10.70	10.57	10.44	10.83	10.50
3:30	.....	10.69								

	19	20	21	22	23	24	25
12 m.	10.70	10.70	10.70	10.63	10.50	10.31	10.50
1 a. m.	10.76	10.70	10.70	10.50	10.44	10.31	10.37
2	10.70	10.70	10.76	10.63	10.44	10.31	10.37
3	10.70	10.70	10.70	10.50	10.44	10.37	10.63
4	11.03	10.70	10.70	10.50	10.44	10.37	10.50
5	10.83	10.70	10.70	10.57	10.50	10.31	10.44
6	10.76	10.70	10.70	10.44	10.44	10.31	10.37
7	10.70	10.70	10.76	10.70	10.44	10.37	10.44

On the other hand, Rud [7] stated that the hemoglobin values are constant and there is no real variation during the day. In this study the variations in a day have been found to be within the limit of error of the method and, as with the total reds, the afternoon depression was not proved to be significant according to the data on hand. Neither were the means of the day, evening and night counts found to be really dif-

TABLE 13.—*Original Data: Total Erythrocyte Counts, 10 to 20 Drops from the Same Pipet, Number Counted in Eighty Small Squares*

Technician A												
1		2		3		4		5		6		
437	441	434	424	421	413	398	401	420	440	432	418	
444	427	452	409	425	424	398	413	430	436	424	429	
465	458	432	431	421	415	419	374	443	430	440	413	
435	431	423	431	405	412	415	397	452	445	434	423	
431	429	455	412	411	408	407	414	433	455	434	423	
442	483	408	436	433	409	395	418	434	433	419	426	
422	443	424	443	399	417	393	399	440	427	413	426	
417	412	442	421	413	413	412	411	435	429	439	424	
420	431	420	426	408	404	414	412	436	426	428	422	
417	425	418	430	419	390	384	401	431	433	419	426	

Technician C					
1		2		3	
477	472	433	403	448	469
476	475	431	439	439	440
482	482	419	418	433	434
475	454	431	415	459	454
456	471	424	425	462	447
457	456	420	450	455	433
466	456	430	430	447	444
455	448	431	437	452	439
459	461	426	418	458	439
451	449	447	418	444	456

Technician D							
1		2		3		4	
488	481	465	468	431	427	421	424
480	483	475	460	425	425	414	424
466	461	476	464	415	426	413	420
485	473	460	458	420	422	431	428
481	472	475	476	427	417	424	424
		468	470				

Technician F							
1		2		3		4	
393	392	386	390	394	393	393	393
393	399	391	390	393	392	394	393
394	392	388	389	394	393	392	393
390	391	391	390	393	394	393	392
391	393	392	391	394	395	394	394

ferent from each other. A drop after meals has not been noticed (confirming Rud [7]), although Marx [32] (1925) described such a reaction after the intake of water.

There is very little literature concerning the variations in hemoglobin values from day to day. Rud,[7] consistent with his belief in the constancy of the total counts, stated that over longer periods of time the variations in hemoglobin determinations are less frequent and

32. Marx, H.: Untersuchungen über den Wasseraushalt, Klin. Wchnschr. **4**:2339 (Dec. 3) 1925.

smaller than those of the red cells. According to Lippincott [33] (1927), the hemoglobin is highest in cold months and lowest after the hot months. In this investigation the hemoglobin values have been found to vary during long periods of time, the wider distribution of the observations being reflected in the larger coefficients of variation. Work is being continued on this phase of the problem in its relation to total counts and cell volumes.

SUMMARY

1. Total erythrocyte counts and hemoglobin determinations vary within the limits of error of the methods for short periods of time.

2. Total erythrocyte counts and hemoglobin determinations do not vary significantly in response to rest, moderate activity or food.

3. There may be real differences between total erythrocyte counts and hemoglobin determinations of separate days or between averages for longer periods.

4. The error inherent in the method should always be a known value in investigations involving data of this kind.

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33. Lippincott, L. S.: Hemoglobin and Erythrocytes in the South, J. Lab. & Clin. Med. **12**:679, 1927.

DIFFERENTIAL DIAGNOSIS OF MEDIASTINAL "TUMORS"

ANALYSIS OF EIGHT VERIFIED CASES *

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In 1888, Hare [1] collected 520 cases of mediastinal disease, over 50 per cent of which were due to tumors, mostly of the malignant type. Riegel,[2] Bennett,[3] Eger,[4] Harris [5] and Steven [6] have written monographs on the subject of intrathoracic and mediastinal tumors. Yet mediastinal tumors continue to awaken keen interest in view of their protean manifestations, their diagnostic difficulties and their generally poor prognosis. A review of the literature indicates that there is not a single pathognomonic symptom or sign on which one can depend in the differential diagnosis of mediastinal masses. As has been repeatedly shown, metastasis elsewhere in the body may initiate and dominate the symptomatology. The eight cases here reported originated in the anterior, middle or posterior mediastinum. We have had several cases of esophageal carcinoma, limited strictly to the posterior mediastinum, which we do not include in this report.

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* From the Departments of Pathology and of Medicine, Albany Medical College and Albany Hospital.

1. Hare, H. A.: The Pathology, Clinical History and Diagnosis of Affections of the Mediastinum, Other Than Those of the Heart and Aorta, with Tables Giving the Clinical History of 520 Cases, Fothergillian Essay, 1888, Philadelphia, P. Blakiston's Son & Company, 1889.

2. Riegel, F.: Zur Pathologie und Diagnose der Mediastinaltumoren, Virchows Arch. f. path. Anat. **49**:193, 1870.

3. Bennett, J. R.: Cancerous and Other Intrathoracic Growths, Their Natural History and Diagnosis, London, J. & A. Churchill, 1872.

4. Eger, J.: Zur Pathologie der Mediastinaltumoren, Inaug. Dissert., Breslau, March 26, 1872.

5. Harris, V. D.: Intra-Thoracic Growths, St. Barth. Hosp. Rep. **28**:73, 1892.

6. Steven, J. L.: The Pathology of Mediastinal Tumors with Special Reference to Diagnosis, London, H. K. Lewis & Company, 1892.

REPORT OF CASES

CASE 1.—*Malignant Endothelioma of the Mediastinum.*

M. W., a white woman, aged 61, a widow, entered the Albany Hospital in the service of Dr. L. Whittington Gorham, Nov. 6, 1925. She complained of fulness in her throat, with marked hoarseness and occasional attacks of choking. There was no history of tuberculosis or cancer in her family. Two years before admission to the hospital she had had pneumonia. Since then she had been having a chronic cough, and had therefore spent the preceding summer in a sanatorium for tuberculosis. The chronic, high-pitched cough had been bothering her for about one and one-half years. It had gradually produced more and more of a choking sensation, as the throat seemed to fill up when she coughed.

The patient was well developed but thin. There were no visible pulsations in her neck, no tracheal tug, no rigidity and no palpable glands. The chest was long

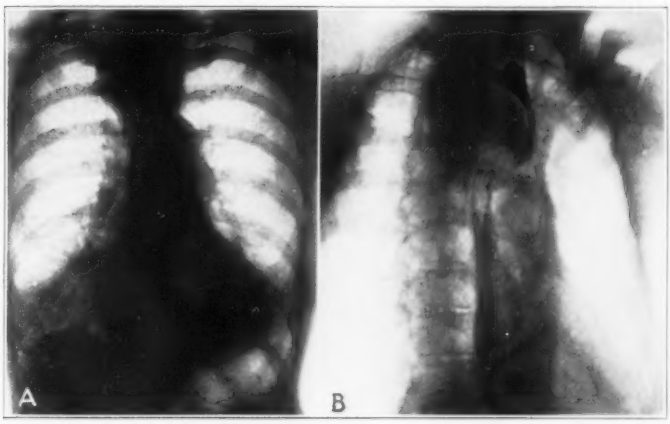

Fig. 1 (case 1).—*A*, anteroposterior roentgenogram showing the mediastinal tumor shadow at the level of the manubrium sterni, extending approximately 3.5 cm. toward the right side of the chest and having a base 7.5 cm. in extent. *B*, right oblique view. Note how the barium-filled esophagus winds around anteriorly over the mediastinal mass.

and symmetrical. Expansion was equal on both sides. The lungs were hyperresonant and the breath sounds normal. The heart seemed slightly enlarged on percussion. The retrosternal dulness across the upper part of the chest measured 11 cm. The abdomen was large and tympanitic. There were no palpable masses. The radial pulses were equal and of good quality.

Examination of the blood revealed: hemoglobin, 90 per cent; red blood cells, 4,776,000; white blood cells, 6,800; polymorphonuclear leukocytes, 67 per cent; transitionals, 3 per cent, and lymphocytes, 31 per cent. The systolic blood pressure was 120 and the diastolic 70. The blood contained 100 mg. of sugar and 32 mg of nonprotein nitrogen per hundred cubic centimeters. The Wassermann test was negative. Urinalysis on one occasion revealed a trace of albumin, no sugar and a

few pus cells. The temperature, pulse and respirations were practically normal throughout the course of the disease.

Roentgen examination showed the lungs to be emphysematous, with no definite evidence of tuberculosis. The heart appeared to be enlarged. At the level of the manubrium of the sternum, there was an oval opaque area extending from the mediastinum a distance of 3.5 cm. into the right side of the chest; its base measured 7.5 cm (fig. 1). This suggested a mediastinal tumor or an innominate aneurysm. The mass had not been evident in three previous roentgen examinations, the last of which was made seven months before. No pulsations were

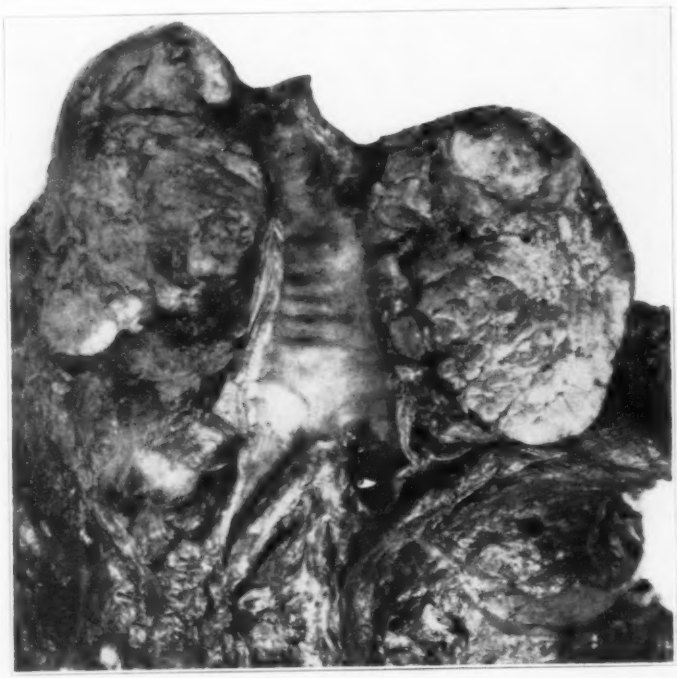

Fig. 2 (case 1).—Posterior view of mediastinum showing the tumor mass bisected and the trachea laid open. The close apposition of the tumor with the trachea above the tracheal bifurcation is evident.

observed under the fluoroscope. When the patient swallowed barium, the esophagus was observed to be anterior to the mass. Thus, fluoroscopy showed no definite suggestive evidence of an aneurysm.

The paroxysms of choking and coughing grew more severe and the patient gradually became weaker. She died on her twenty-seventh day in the hospital.

Necropsy was performed nine hours post mortem. The veins of the mediastinum and chest wall were much dilated and of a dark color. Thymic tissue was not seen, and the anterior mediastinum contained a normal amount of fat. In the superior mediastinum behind the trachea, a firm mass about the size of a

small lemon could be palpated. It lay slightly to the right of the midline, and its upper border reached about to the level of the sternoclavicular joint. The thoracic organs were removed en masse. Viewed from behind, the esophagus wound around the left side of the tumor and was flattened as it passed over it. The arch of the aorta was pushed forward by the tumor. The trachea lay anteriorly and was only slightly compressed (fig. 2). The tumor was an encapsulated

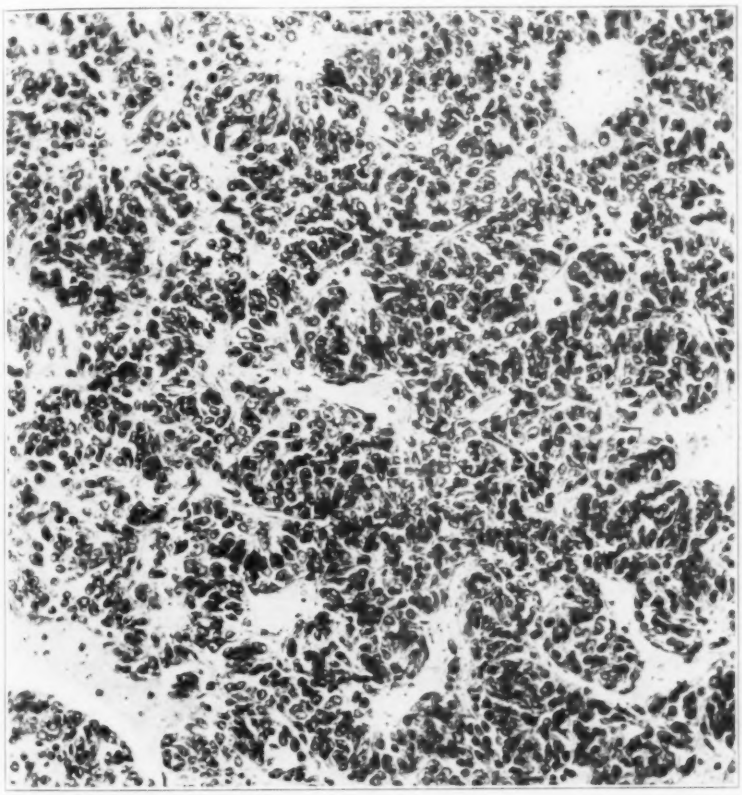

Fig. 3 (case 1).—Photomicrograph of the endothelioma. Note the numerous capillary channels around which the tumor cells are arranged in a perithelial manner. Hematoxylin and eosin stains; × 208.

firm mass, not intimately connected with any of the important mediastinal structures. Microscopic examination showed it to be a malignant endothelioma, probably of vascular origin (fig. 3). There was no tumor metastasis in the thoracic lymph nodes. The thyroid showed an adenomatous condition with much chronic inflammation.

Comment.—Endotheliomas of the mediastinum are infrequently observed. It is interesting to note that this patient dated the onset of her trouble to pneumonia which was followed by a chronic irritating cough. Although her symptoms dated back over one and one-half years, the mediastinal tumor did not become evident until seven months before admission to the hospital, as shown by the repeated roentgen examinations for suspected pulmonary tuberculosis. In the earlier stages of paratracheal or parabronchial tumors, it is not unusual that pulmonary tuberculosis or other chronic respiratory diseases should be suspected, since the only symptom may be an unexplained cough. In a study of thirty-nine cases, Bennett [3] found that the most frequent of early local symptoms was some indication of bronchial irritation, such as cough, whether the lungs had or had not been implicated earlier. If expectoration is present it is usually mucoid. The next earliest symptom is dyspnea on exertion. Physical signs are generally lacking entirely until the condition has made considerable progress. Hampeln [7] expressed the belief that the first sign of mediastinal new growth is a disturbance of the venous-lymphatic flow, causing cyanosis of the face and edema of the neck.

Romano, Ruiz and Waldorp [8] reported a case of hemangio-endothelioma of the superior anterior mediastinum with metastasis to the left side of the brain, the liver, both suprarenals and both kidneys. The symptoms were predominantly neurologic, and only in the later stages did the intrathoracic tumor become evident by the retraction of the right half of the chest, impaired respirations, diminished resonance, abolished vibrations and edema of the neck. Brustolon and Parere's [9] case presented a picture of compression of the anterior mediastinum with a sense of imminent death. At autopsy, an endothelioma of the mediastinum was found which had invaded the pleura and right lung. Heuer [10] reported an interesting case of pleural endothelioma which presented itself externally just below the inferior angle of the left scapula. Positive diagnosis before operation was possible by the aspiration of tumor cells.

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7. Hampeln, P.: Ueber die ersten Anzeichen mediastinaler Neubildungen, Deutsche med. Wchnschr. **47**:1052, 1921.

8. Romano, N.; Ruiz, F. N., and Waldorp, C. P.: Hemangioendotelioma intra-capilar con localización predominante mediastínico pulmonar superior derecho. Con síndrome de epilepsia Jacksoniana del lado derecho y luego hemiplegia dolorosa con afasia motriz y metástasis múltiples, Rev. Asoc. méd. argent. **31**:748, 1919.

9. Brustolon, A., and Parere, V.: Su di un caso di endotelioma del mediastino, Arch. di pat. e clin. med. **6**:557, 1927-1928.

10. Heuer, G. J.: Intrathoracic Tumors: Experiences with 8 Cases of Tumor of the Thoracic Wall, Pleura and Mediastinum, Ann. Surg. **79**:670, 1924.

CASE 2.—*Medullary Carcinoma, Primary in the Mediastinum, with Extension to the Lungs and Metastasis to the Brain and Cerebellum.*

L. J., a white man, aged 42, American, married, a creamery manager, entered the Albany Hospital under the care of Dr. Arthur H. Stein on March 1, 1927. He complained of a sore throat and inability to speak above a whisper. This began with a slightly sore throat about five weeks before admission to the hospital. Shortly afterward, he had difficulty in talking.

His health had usually been good. At times, he had had some headache and dizziness. His eyes had given him no trouble. Recently he had had vomiting. He had become more and more restless, so that he kept his arms and legs in motion

Fig. 4 (case 2).—This roentgenogram shows the mediastinal shadow increased in width.

much of the time and occasionally had clonic movements of both upper and lower extremities.

It was difficult to make a satisfactory physical examination, because he was drowsy much of the time and unable to focus his attention. He had definite aphasia. All responses were delayed. He was apt to give the same answer to several different questions. He was entirely helpless and had to be fed at all times. There was complete loss of sphincteric control.

Neurologic examination by Dr. LaSalle Archambault revealed that the pupils were under the effect of a cycloplegic. The outlines of the disk were ill defined and the veins somewhat full. Ocular excursion was unrestricted. There was a

weakness of the facial musculature on the right side. The tongue deviated to the right. The upper extremities showed bilateral atonia, more marked on the right. There was no ataxia in the arms, but a definite intention tremor on the right. Reflexes of both upper extremities were equal. The abdominal and cremasteric reflexes were decidedly more active on the left side than on the right.

The lower extremities showed paresis, slightly more marked on the right. Knee and ankle jerks seemed more active on the right. There was a partial clonus on the right. No Babinski or Oppenheim sign was present on either side.

Fig. 5 (case 2).—Posterior view of the mediastinum showing the tumor in the angle of the tracheal bifurcation.

Four days later, the patient was found to be looking persistently to the left. There was a definite spasm of the posterior cervical muscles. The patient continued to speak in a whisper and was definitely disoriented.

A roentgen examination made at this time showed the mediastinum increased in width and the lung markings accentuated (fig. 4). Because of the mental condition of the patient, it was difficult to get him to swallow barium to determine whether or not the mass encroached on the posterior mediastinum.

His temperature was subnormal most of the time; the pulse rate ranged between 70 and 140 and the respirations were increased to 65 per minute. His urine was normal. He died eight days after admission to the hospital.

At autopsy, twenty minutes post mortem, an irregularly nodular white tumor mass, approximately 8 by 6 by 4 cm., was found in the superior mediastinum. The greater part of the tumor lay at the bifurcation of the trachea and directly beneath the arch of the aorta (fig. 5). The descending portion of the arch was displaced slightly to the left. On sectioning, the tumor showed a hard white

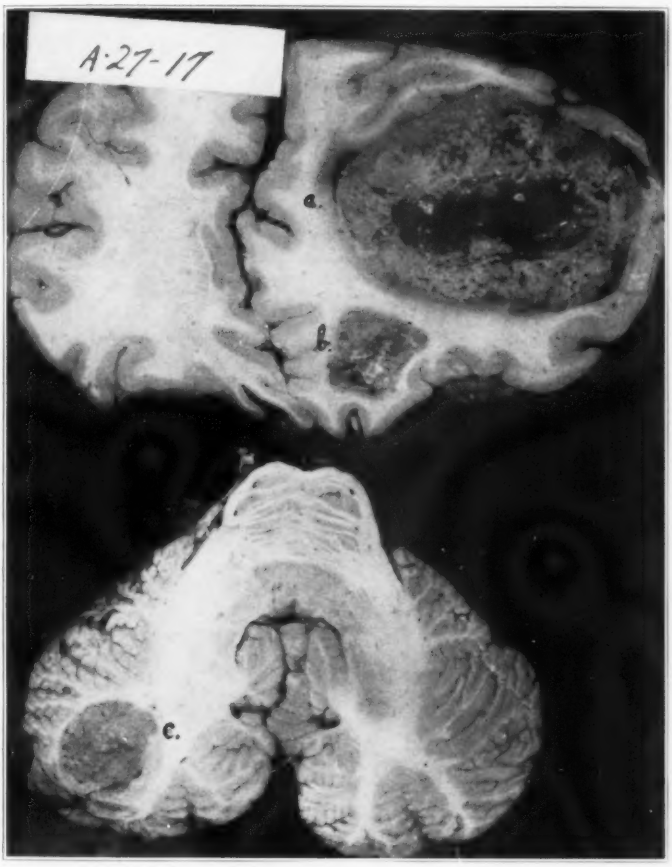

Fig. 6 (case 2).—The three metastatic tumor nodules are shown in the cerebrum (*a* and *b*) and cerebellum (*c*).

granular surface with numerous small foci of anthracosis. The trachea, esophagus and aorta were not involved by the tumor mass which, however, invaded the wall of the superior vena cava and projected into the lumen as flat tumor nodules, 0.5 to 2 cm. by 2 to 4 cm. The apex of each lung was adherent to the tumor mass by direct extension of the growth. The remainder of both lungs showed bronchopneumonia and edema. The heart was not involved by the tumor.

The brain weighed 1,690 Gm. The meningeal veins stood out prominently, owing to their marked engorgement. The left hemisphere throughout was more voluminous than the right. There was a striking atrophy of both temporal lobes, as shown by the unusual width of the fissures and the corresponding narrowing of the gyri. There was some evidence of intracranial hypertension in the abnormal prominence of the amygdalae. Frontal sectioning showed that the tumor nodule visible over the convexity as a dark round area, about 3 cm. wide, extended deeply into the white matter to within 1.5 cm. of the mesial surface of the frontal lobe and 2 cm. from the basilar surface. Another nodule, 2 by 2.5 cm., distinctly

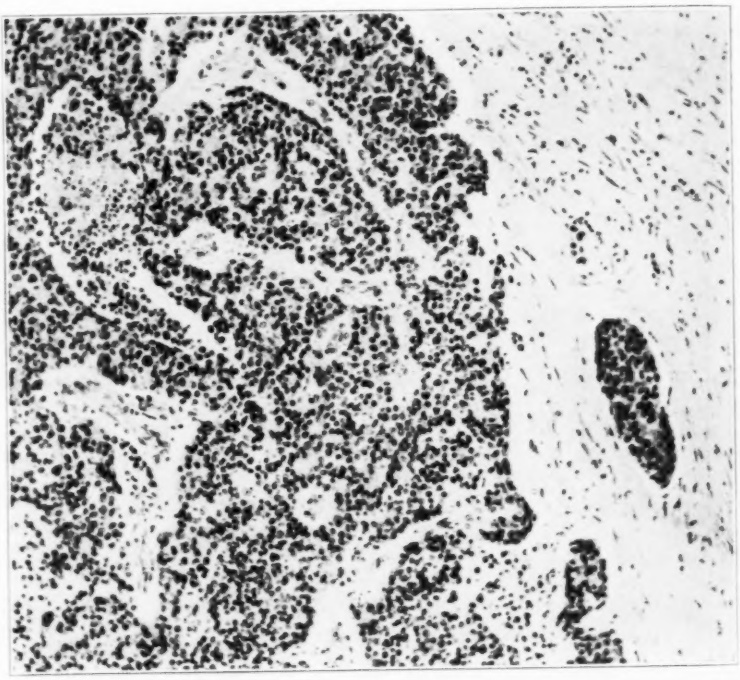

Fig. 7 (case 2).—Photomicrograph of the mediastinal tumor showing the highly cellular, medullary character of the growth. Hematoxylin and eosin stains; × 137.

oval-shaped and well demarcated, occupied the subcortex of the gyrus rectus. The larger tumor mass extended backward to the level of the anterior horns of the lateral ventricles which were considerably distended. A third tumor nodule, 2 by 2.2 cm., was found immediately beneath the cortex of the left semilunar lobule of the cerebellum (fig. 6).

Microscopic sections of the mediastinal tumor, the extensions to the lungs and the metastatic nodules in the brain and cerebellum showed medullary carcinoma (fig. 7).

Comment.—This patient was admitted to the neurologic service as the symptomatology pointed to a left-sided tumor of the brain. Primary mediastinal tumors not infrequently metastasize to the brain or invade the vertebra and spinal cord. When neurologic symptoms predominate, and especially when symptoms of intrathoracic pressure are masked or do not appear until late, these patients have sometimes been operated on for primary tumor of the brain.

Mix [11] reported a case of carcinoma of the posterior mediastinum which pressed on the inferior vena cava below the entrance of the hepatic vein. From a study of the literature, he found that the ratio of primary to secondary mediastinal malignant tumors is 8:1 and the ratio of benign to malignant mediastinal tumors 1:10. Thus, mediastinal tumors are more apt to be primary and malignant. Statistics differ as to which is more common. Carcinomas have been found more frequently by Hare,[1] Mix and Maxwell,[12] and sarcomas more frequently by Harris,[5] Steven,[6] Rosenson [13] and Kott.[14]

Case 3.—*Thymoma, with Direct Extension to the Pericardium, Heart, Pleura and Diaphragm and Metastasis to the Lungs.*

D. B., an Italian laborer, aged 19, who had been in this country for a year, was admitted on Oct. 16, 1923, to the Albany Hospital in the service of Dr. Thomas Ordway, complaining of extreme difficulty in breathing. He had been in good health until eighteen days before admission to the hospital, when he stayed at home because of a feeling of weakness, malaise and feverishness. For the next ten days, he was in bed most of the time. Five or six days before admission, after swa" wing a piece of steak at dinner, he had a choking spell, turned blue and could not get his breath. This attack lasted for fifteen minutes. On the third and second days before admission, he had similar short attacks of dyspnea and cyanosis. On the day of admission, the distress recurred, and this time persisted.

Examination showed a well developed and well nourished youth sitting up in bed, with his head thrown back in extreme dyspnea and marked cyanosis. He perspired profusely and constantly pointed to his throat. The throat was dry and red with a few small white spots scattered over the posterior pharyngeal wall. The left arm was slightly swollen. The pulse was weaker in this arm than in the right. The heart sounds were of good quality, with no murmurs. Over the left lung there was dulness, with diminished breath sounds posteriorly. Over the base of both lungs coarse moist râles were present.

11. Mix, C. L.: Mediastinal Tumors: Full Discussion of Mediastinal Tumors both Benign and Malignant with Classification; Symptomatology; Autopsy, M. Clin. North America **3**:1507, 1920.

12. Maxwell, J.: Primary Malignant Intrathoracic Tumors, J. Path. & Bact. **33**:233, 1930.

13. Rosenson, W.: Neoplasms of the Mediastinum in Infancy and Childhood: Report of a Case of Ganglioneuroma of the Mediastinum in a Girl of 8 Years, Am. J. Dis. Child. **26**:411 (Nov.) 1923.

14. Kott, B.: Ueber Angiosarkome des Mediastinums, Deutsche med. Wchnschr. **48**:1042, 1922.

The white blood cell count was 23,380. The temperature was 99 F., the pulse rate 120 and respirations 28.

A roentgen examination was not made, as the patient was moribund. The respiratory difficulty and cyanosis increased rapidly. The patient died five hours after admission to the hospital.

At autopsy, four hours post mortem, a primary mediastinal tumor was found, markedly compressing the trachea and esophagus. This tumor (fig. 8) probably

Fig. 8 (case 3).—Anteroposterior view of the thymic tumor which has been bisected, exposing the pericardial cavity. The heart has been removed. The trachea is seen as a V-shaped notch at the upper end of the photograph. The lobular character of the tumor which fills the entire anterior mediastinum is evident.

arose in the thymus because of its position, its lobulated structure and the nature of the type cell which is encountered in the so-called malignant thymoma or thymic lymphocytoma. Microscopic examination showed metastases in the lungs as well as a direct extension to the pericardium, heart, adjacent pleura and diaphragm (fig. 9).

Comment.—Tumors of the thymus continue to hold the interest of clinicians and pathologists alike. They are no longer considered rare. One necessarily thinks of thymic tumors when symptoms of mediastinal pressure in the young are associated with anterior bulging of the chest wall. In this case, the sternum was neither pushed forward

Fig. 9 (case 3).—Photomicrograph showing that the thymic tumor cells have densely infiltrated the subepicardial fat and are invading the myocardium. Hematoxlin and eosin stains; × 194.

nor invaded by the anterior mediastinal tumor. In an exhaustive review of the literature, Crosby [15] found that the sternum was actually invaded in 10.1 per cent of the cases of thymic lymphosarcoma.

15. Crosby, E. H.: Personal communication to the authors. This same case is being reported in detail by him.

Danisch and Nedelmann [16] reported a case in a child in whom a malignant thymoma metastasized to the central nervous system and produced symptoms of meningeal irritation with a pleocytosis of tumor cells in the cerebrospinal fluid. In one of Delessert's cases,[17] a lymphosarcoma of the anterior mediastinum penetrated the lumen of the right internal jugular vein and superior vena cava, forming smooth, pink, slightly projecting patches on the internal aspect of these vessels. Delessert expressed the belief that one should be extremely reserved in affirming the thymic origin of malignant tumors of the anterior mediastinum when the characteristic glandular elements of the thymus are absent in the tumor. However, one must remember that although the presence of structures resembling Hassall's corpuscles (well preserved or degenerated and calcific) is of great aid in determining the origin of anterior mediastinal tumors from the thymus, their absence does not mean that they may not have been there in the early stages of the growth of the tumor process. Furthermore, Hassall's corpuscles may be found if a lymphosarcoma of the mediastinal lymph nodes extensively infiltrates the anterior mediastinum.

As emphasized by Jacobson,[18] the clinical diagnosis of thymomas is difficult. The correct diagnosis rests on biopsy or autopsy. In the thymoma described by Meeker,[19] repeated biopsies finally revealed the nature of the tumor, which was later confirmed at autopsy.

CASE 4.—*Hodgkin's Disease of Cervical and Mediastinal Lymph Nodes with Invasion of the Trachea and Metastasis to the Colon and a Meckel's Diverticulum.*

A. J., a white man, aged 41, American, married, a detective, entered the Albany Hospital on Sept. 12, 1921, in the service of Dr. Arthur W. Elting, for the removal of a tumor on the left side of the neck. This had been noticed first about a month before admission to the hospital, and during the preceding week it had increased rapidly in size to that of a large hen's egg. The mass was not painful. He had always been in good health except for typhoid fever and pneumonia. His only operation was a tonsillectomy performed during childhood. He had maintained his average weight for some time.

The teeth were in poor condition. On the left side of the neck were irregularly outlined masses, extending from about 1 inch (2.5 cm.) below the left ear along the sternocleidomastoid muscle to about 1 inch above the clavicle. They were fairly

16. Danisch, F., and Nedelmann, E.: Bösartiges Thymom bei einem 3½ jährigen Kind mit eigenartiger Metastasierung ins Zentralnervensystem, Virchows Arch. f. path. Anat. **268**:492, 1928.

17. Delessert, E.: A Clinical Study of Malignant Tumors of the Anterior Mediastinal and Thymic Origin, Internat. Clin. **2**:127, 1922.

18. Jacobson, V. C.: Primary Carcinoma of the Thymus, Arch. Int. Med. **31**: 847 (June) 1923.

19. Meeker, L. H.: Malignant Thymoma: Report of a Case, Arch. Path. **5**:928, 1928. This same case was reported later by Herriman and Rahte (Malignant Thymoma with Metastases, Am. J. Path. **5**:29, 1929).

movable over the underlying structures, but seemed adherent to the skin. Accentuated breath sounds and a few small crepitant râles were heard over the apex of the left lung.

A preoperative specimen of urine had a specific gravity of 1.028, and contained albumin but no sugar. The heavy sediment consisted of pus cells, mucus and squamous epithelial cells.

The tumor mass in the neck was removed and the patient was discharged five days later. On microscopic study, this tumor appeared to be an atypical lymphoma.

Almost nine months later, the patient was readmitted in a moribund condition. During his three days in the hospital, his temperature ranged between 99 and 103 F.; the pulse rate averaged 120 and the respirations 45 per minute. The clinical diagnosis was sarcoma of the neck with metastasis to the mediastinum.

Necropsy was performed five hours post mortem. The body was that of a well developed and somewhat obese adult. The left arm was greatly swollen, owing to a marked cellulitis, superficial necrosis and marked edema. Over the tumor mass in the left side of the neck there was a discharging ulcerated area with brawny induration and brownish discoloration of the skin. This discoloration had extended down over the left side of the chest. The enlarged, opaquely white, firm cervical and mediastinal lymph nodes were matted together; the tumor process infiltrated out into the surrounding tissues. Supraclavicular, inguinal and mesenteric lymph nodes were also markedly enlarged. The spleen was not involved. Both lungs showed an acute bronchopneumonia with agonal thrombosis and infarction. Detailed microscopic study showed that this was a case of Hodgkin's disease of the cervical and mediastinal lymph nodes, with invasion of the trachea and adjacent tissues and with metastasis to a Meckel's diverticulum, the colon and mesenteric and inguinal lymph nodes.

Comment.—It is generally accepted that although Hodgkin's granuloma may be suspected clinically, the diagnosis rests on the biopsy. Simonds,[20] in his general review, found that the most extensively invasive cases of Hodgkin's disease have occurred in the mediastinum and have been thought by many to have originated from the thymus. In this country, Ewing [21] particularly expressed the belief that the invasive form of mediastinal Hodgkin's disease is in reality a thymic tumor. Lyon [22] reported an unusual case of mediastinal Hodgkin's granuloma, with perforation of the anterior chest wall in addition to widespread metastasis. Ewing pronounced Lyon's case another example of thymoma belonging to the Hodgkin's class.

CASE 5.—*Neurofibroma of the Mediastinal and Inferior Cervical Regions Undergoing Sarcomatous Changes in a Case of von Recklinghausen's Disease.*

20. Simonds, J. P.: Hodgkin's Disease: General Review, Arch. Path. **1**:394 (March) 1926.

21. Ewing, J.: The Thymus and Its Tumors: Report of 3 Cases of Thymoma, Surg. Gynec. Obst. **22**:461, 1916; Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 923.

22. Lyon, M. W.: Case of Mediastinal Hodgkin's Granuloma with Perforation of the Chest Wall, Am. J. M. Sc. **158**:557, 1919.

W. F., a white man, aged 28, American, was admitted on Dec. 8, 1927, to the service of Dr. George E. Beilby, Albany Hospital, with the chief complaint of soreness and "lumps" on both sides of his neck. Outside of the usual diseases of childhood, his general health had been excellent. His tonsils and adenoids had been removed when he was 21 years of age. For the preceding ten years, he had noticed a "goiter," which had remained symptomless until about five months before admission to the hospital. At that time, he noticed a "drawing" and an ache in the right side of his neck. The swelling in the neck had not increased in size; the patient thought it had grown slightly smaller. He had headaches at

Fig. 10 (case 5).—The superior mediastinal shadow is much widened, with projection of the tumor mass into the right pleural cavity. The trachea is displaced toward the left.

night while at work in the railroad yards. There had been no tremor of his hands, no sweating or flushing and no loss in weight.

Physical examination revealed a well developed and well nourished young man. There was no motor restlessness. The skin was soft and cool, and showed no flushing. It showed, however, numerous soft tumors, varying in size from about 2 mm. to 5 cm. in diameter. Some of these cutaneous nodules were sessile; others were pedunculated. They were irregularly distributed all over the body. The skin also showed an irregular brownish pigmentation. A few of these pigmented areas measured from 2 to 5 cm. in their largest diameter, but most of them looked like freckles.

The skull was symmetrical. A slight tenderness was present over the right mastoid process. There was some fulness on the right side of the pharynx as though some swelling from the outside were pressing inward. The neck was large and asymmetrical, owing to the presence of large bilateral masses. The right mass was larger, and extended almost to the tip of the mastoid process, beyond the

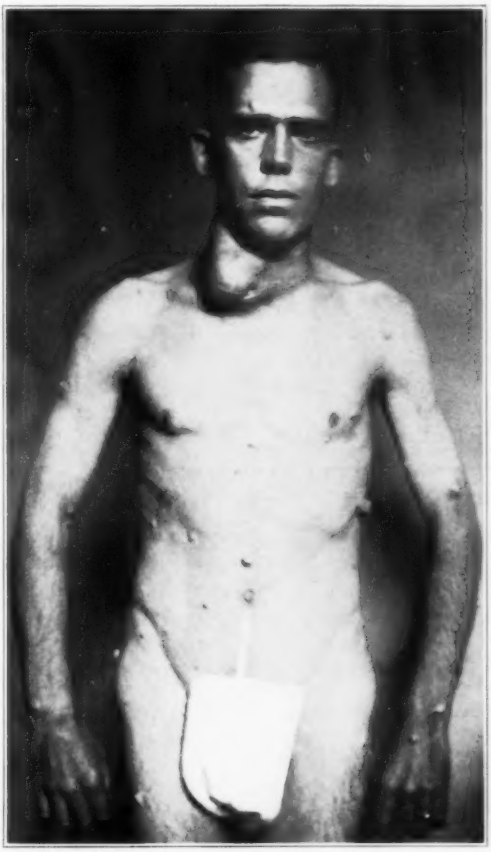

Fig. 11 (case 5).—Patient with von Recklinghausen's disease. Note the large, almost pendulous, tumor mass in the right side of the neck. This is the externally visible portion of the mediastinal growth shown in figure 10.

midline and down behind the clavicle. Its lower pole was not palpable; pressure on the lower edge caused coughing. The left mass was not so large and was connected across the midline with that on the opposite side. Its lower pole was also not felt. The trachea was markedly displaced to the left. The tumor masses were firm and somewhat irregularly lobulated. A loud systolic bruit could be

heard over the large cervical mass. In addition, many small indurated, discrete nodules were present superficially on both sides of the neck. There were large dilated veins over the right side of the neck and shoulder.

The chest was well developed. The right supraclavicular fossa was almost obliterated by the large tumor mass. The left clavicle appeared more prominent. There was a slight increased convexity of the right side of the chest posteriorly. Chest expansion was good and appeared equal. The lungs were resonant everywhere except for a slight impairment at the right apex. Breath sounds were loud and bronchovesicular, especially at the right apex anteriorly and posteriorly. With the exception of many bilaterally enlarged, indurated nodules in the cervical, axillary, epitrochlear and inguinal regions, examination of the rest of the body yielded no remarkable results.

Roentgen examination revealed a large mass in the mediastinum, extending from the base of the heart into the neck and measuring 14 cm. in its greatest transverse diameter. The trachea was displaced toward the left and apparently compressed (fig. 10).

The preoperative urinalysis gave no unusual results. The Wassermann test of the blood was negative.

At operation, an exploratory thyroid incision was made. The tumor mass, which extended behind the manubrium sterni, was soft. As total removal was impractical, only a biopsy was performed. The pathologic report was edematous fibroma. The patient was discharged with instructions to return for frequent observation.

He was seen again about two months later. Except for the operative scar, the physical observations were essentially the same as before (fig. 11).

About seven months later, the right side of the neck became enormously swollen and fluctuant. On incision of the fluctuant area, degenerating and necrotic material was obtained. A roentgen examination at that time showed a large mass projecting from the neck into the right side of the chest, which displaced the trachea toward the left side. This area measured approximately 13 by 12 cm.

His third and last admission was about ten months after the first. The chief complaint at this time was pain and aching in the left side of his head and in the left shoulder. In the neck were large, asymmetrical, bilateral masses which were more prominent on the right side. The lower pole disappeared behind the sternum. Pressure over this region caused coughing. The left clavicle was still slightly more prominent. Both supraclavicular fossae were now obliterated.

At the second operation, the tumor masses had greatly increased in vascularity. The portion projecting above the sternum was myxomatous and friable. Anteriorly it crossed the midline to the left, evidently invading adjacent muscles. Bleeding was controlled by sutures. Two drains were inserted in the cavity formed by the removal of part of the tumor mass. The pathologic report this time was spindle cell sarcoma, rapidly growing and infiltrating adjacent structures.

After leaving the hospital, the patient continued to decline, and died a month later. Autopsy was not permitted. The patient probably died of internal metastasis, judging from the microscopic evidence of invasion of blood vessels by the sarcomatous cells.

Comment.—This case has been studied elsewhere in much more detail by one of us (K. H.).[23] Sixty-four similar cases were collected

23. Hosoi, K.: Multiple Neurofibromatosis (von Recklinghausen's Disease), with Special Reference to Malignant Transformation, Arch. Surg. **22**:258 (Feb.) 1931.

from the literature and the following conclusions were drawn: Malignant transformation takes place in about 13 per cent of all cases of von Recklinghausen's disease. When this happens, the tumor grows rapidly and tends to recur locally even after repeated operative measures. Metastasis is usually late and frequently absent, but may occur early. In some cases, the mere extirpation of a malignant tumor or even a benign one appears to stimulate another neurofibroma distantly located to undergo sarcomatous transformation. Prognosis is poor, the patient succumbing to cachexia and postoperative complications if not to the metastasis.

Banse,[24] in 1908, reported an interesting case of fibrosarcoma of the posterior mediastinum with invasion of the vertebrae and the spinal canal, producing the chief symptoms of progressive weakness in both lower extremities. Grawitz' fifth case [25] is somewhat similar in that a fibrosarcoma lying between the right apex of the lung and the esophagus infiltrated the vertebral column and compressed the spinal cord. As in our second case, the neurologic symptoms may tend to dominate the picture, drawing one's attention away from the mediastinum. Recently, Crile and Ball [26] reported three cases of primary neurogenic tumors of the neck and the mediastinum and collected sixteen similar cases from the literature. They expressed the belief that surgical removal is the only treatment for this type, as radium and roentgen rays do not stop its further growth. We should like to stress the point that an operative attack on mesoblastic tumors of nerve trunks, especially in cases of von Recklinghausen's disease, must be undertaken with great caution.

Case 6.—*Epidermoid Carcinoma of the Right Eparterial Bronchus with Invasion of the Vertebra, Spinal Cord and Nerve Roots.*

L. M., a man, aged 53, Hebrew, a clothes presser, was admitted on Oct. 20, 1928, to the service of Dr. Thomas Ordway. He had been in fair health until six months previously, when he acquired a cold with bronchitis and a cough which was worse at night. Two months later, he was obliged to stop working as he suffered spells of weakness and dizziness. He was told he had a "spot in his lung," revealed by a roentgen examination made elsewhere. He rested in the mountains for several months, but returned because of a pain in his right shoulder which he understood was "pleurisy." The cough continued to annoy him whenever he lay down, and the throbbing pain in the muscles and soft parts around the right shoulder and axilla became so severe and constant as to interfere with his sleep. At no time did he have night sweats, hemoptysis or much expectoration.

24. Banse, J.: Ueber intrathoracische Fibrome, Neurome und Fibrosarkome, Inaug. Dissert., Greifswald, Feb. 1, 1908.

25. Grawitz, P.: Demonstration einer neuen Gruppe intrathoracakaler Tumoren (Neuro-Fibrosarkome), Deutsche med. Wchnschr. **34**:1123, 1908.

26. Crile, G. W., and Ball, R. P.: Primary Nerve Tumors of the Neck and Mediastinum, Surg. Gynec. Obst. **48**:449, 1929.

Anorexia became marked. Frequency of urination occurred both day and night. His past history was uneventful.

The patient was poorly developed and undernourished. The upper third of the right side of the chest was retracted and expansion was diminished over this area. There seemed to be atrophy of the right pectoralis major, with definite tenderness over the soft parts of the right shoulder. Definite dulness was present over the upper third of the right side of the chest anteriorly, with markedly increased vocal and tactile fremitus. Breath sounds were increased over the upper third of both lungs, being particularly noticeable from the third to the sixth dorsal vertebra. The rest of the physical examination was not significant except that the prostate was moderately enlarged; the right lobe was firmer than the left, although not tender.

Fig. 12 (case 6).—The roentgenogram shows that approximately 8 cm. of the fourth rib has been destroyed just distal to the head with erosion of the right lateral border of the third and fourth dorsal vertebrae. The diminished transmission of the rays in the right upper lobe is due to tumor infiltration of the lung parenchyma.

The patient's temperature ranged between normal and 101 F. Numerous examinations of the sputum revealed no tubercle bacilli. The blood chemistry and urinary observations were normal. Tests of kidney function gave normal results. The leukocyte count was 9,200. The Wassermann test was negative.

Roentgen examination showed that the right lateral borders of the third and fourth dorsal vertebrae were not clearly defined and that the trachea deviated toward the right (fig. 12). It was felt that these observations in the vertebrae suggested pressure from without.

Neurologic examination by Dr. LaSalle Archambault revealed that the facial musculature was relaxed on the right side when at rest. The pupils were slightly

irregular, but reacted actively. The vagus, glossopharyngeal and spinal accessory nerves were apparently normal. There was considerable atrophy of the spinati, rhomboids, pectorals and biceps on the right side. Active movement was about normal in range, with good resistance to passive motion. The scapulohumeral, pectoral, tricipital and radial reflexes were all active. There were no objective sensory losses in the upper extremities. The right pulse was more voluminous than the left. The lower extremities were normal. These observations, together with the roentgen report, were suggestive of a posterior mediastinal lesion com-

Fig. 13 (case 6).—The trachea and bronchi have been opened posteriorly to show the compression of the right eparterial bronchus by the tumor which projects slightly into the lumen of this bronchus (arrow). Note the large tumor masses in the angle of the bifurcation of the trachea.

pressing the spinal cord and to some extent encroaching on the efferent spinal nerve roots of the superior thoracic region of the cord.

About five weeks after the patient entered the hospital a laminectomy was performed for relief from the intolerable pain. The posterior nerve roots were sectioned from the sixth cervical to the sixth thoracic. A specimen removed from the spinal canal at this time revealed a squamous cell carcinoma, invading the bone and soft tissues.

The patient responded well to the operation and had some relief from pain. His cough, however, continued to be a disturbing factor. He was up and about

the ward until about seven weeks after the operation, when paraplegia of the lower extremities with loss of sensation suddenly developed.

Neurologic examination at this time showed that there had developed, rather acutely, a transverse syndrome with flaccid paraplegia, sphincteric disturbance, greatly weakened tendon jerks and loss of position, pain and thermal sensibility in the lower extremities. This complication was felt to be due to myelomalacia resulting from thrombosis of the anterior spinal artery or, more probably, to compression or infiltration by the neoplasm.

The patient had more and more difficulty in breathing and died of pulmonary edema on the fifty-third day following the operation.

Necropsy was performed one hour after death. A mediastinal tumor mass was found extending over the dome of the right thoracic cavity and down its posterior wall to about the level of the sixth rib, almost as far as the posterior axillary line (fig. 13). The tumor could be seen to cover and invade the vertebral bodies at the level of the third and fourth thoracic vertebrae. The thoracic aorta, trachea and esophagus were not involved. Microscopic examination showed an epidermoid carcinoma of the right eparterial bronchus with invasion of the thoracic vertebrae, of the cord itself and of the nerve trunks with marked compression myelitis. Mediastinal and bronchial lymph nodes were infiltrated with metastatic tumor growth.

Comment.—Weller,[27] in his general review of the pathology of the subject, stated that primary carcinoma of the lung is rarely diagnosed at a sufficiently early stage to allow for successful surgical intervention, but that the diagnosis is being made more frequently on the living patient than at autopsy. Shennan,[28] like Weller, stressed the preponderance of metastasis to the central nervous system. According to Lubarsch,[29] tumor of the brain, apoplexy and progressive paralysis have been diagnosed frequently in these cases of pulmonary carcinoma with central metastasis. Indeed, Fried[30] and Weller stated that the frequency of metastases to the central nervous system as found at autopsy is paralleled by the frequency of clinical cases in which such metastases dominate the picture and lead to erroneous diagnoses. This frequent occurrence of cerebral metastasis has been attributed to the absence of a barrier between the lungs and the brain.

In our case, the confirmatory diagnosis was made by the finding of squamous cell carcinoma in the specimen removed from the spinal canal at the time of laminectomy. In the light of clinical and roentgen

27. Weller, C. V.: The Pathology of Primary Carcinoma of the Lung: General Review, Arch. Path. **7**:478 (March) 1929.

28. Shennan, R.: Tumors of Mediastinum and Lung, J. Path. & Bact. **31**:365, 1928.

29. Lubarsch, O.: Einiges zur Sterblichkeits- und Leichenöffnungsstatistik, Med. Klin. **20**:299, 1924.

30. Fried, B. M.: Primary Carcinoma of the Lungs: Further Study with Particular Attention to Incidence, Diagnosis, and Metastases to the Central Nervous System, Arch. Int. Med. **40**:340 (Sept.) 1927.

observations, the pathologic examination usually confirms the diagnosis by examination of the sputum or pleural fluid for "tumor cells," by examination of the specimen obtained by probatory puncture or through the bronchoscope, and by examination of the superficial lymph nodes containing the metastasis.

If in a case of suspected mediastinal tumor the expectorated or aspirated material contains a large amount of pavement epithelium and fine hairs, the diagnosis of dermoid cyst or teratoma of the mediastinum is suggested. This subject has been exhaustively treated in the excellent papers of Dangschat,[31] Morris,[32] Christian,[33] Hertzler,[34] Harris,[35] Murphy,[36] and Smith and Stone.[37] It is to be borne in mind that these tumors of congenital origin can undergo carcinomatous or sarcomatous transformation. They can be successfully enucleated if malignant changes have not yet taken place.

CASE 7.—*Retrosternal Adenomatous Goiter and Accessory Thyroid in a Case of Enlarged Persistent Thymus.*

W. E., a white man, aged 36, American, single, a clerk, was admitted on May 14, 1929, to the service of Dr. George E. Beilby for a thyroidectomy. Two months before admission to the hospital he first noticed that his heart action was more rapid than previously. At that time there appeared also an increasing dyspnea and excessive perspiration. He had had pneumonia twice within the previous three years, in addition to tonsillitis, influenza and bronchial asthma.

It is interesting to note that his mother had a thyroidectomy the preceding year for exophthalmic goiter and that his sister had a subtotal thyroidectomy also for exophthalmic goiter a month previous to his admission.

After a course of compound solution of iodine, a bilateral subtotal thyroidectomy was performed on the tenth day of his stay in the hospital. At this time, the edematous right lobe of the thyroid was exposed with difficulty as about three fourths of it lay underneath the clavicle. It measured 4 inches (10 cm.) in the largest diameter. The left lobe was similar to the right. Microscopic examination showed it to be an adenoma of the thyroid with degenerative changes.

A few hours after the operation, the patient's temperature, pulse rate and respiratory rate began to rise. In two days, he died of acute bronchopneumonia.

31. Dangschat, B.: Beiträge zur Genese, Pathologie und Diagnose der Dermoidcysten und Teratome im Mediastinum anticum, Beitr. z. klin. Chir. **38**:692, 1903.

32. Morris, R. S.: Dermoid Cysts of the Mediastinum, M. News **87**:404, 438, 494 and 538, 1905.

33. Christian, H. A.: Solid Teratomata of the Mediastinum, J. M. Research **16**:275, 1907.

34. Hertzler: Dermoids of the Mediastinum, Am. J. M. Sc. **152**:165, 1916.

35. Harris, I. B.: Mediastinal Dermoid with Report of Case, Ohio State M. J. **15**:547, 1919.

36. Murphy, J. T.: Dermoid Cysts in the Thorax, with a Review of the Literature, J. Radiol. **3**:8, 1922.

37. Smith, L. W., and Stone, J. S.: Tumors of the Mediastinum in Children, Ann. Surg. **79**:687, 1924.

Necropsy was performed one and one-half hours post mortem. There was acute bronchopneumonia in both lungs. The right lung showed five lobes, instead of the usual three. The superior mediastinum was enlarged, measuring 7 cm. across and 10 cm. in depth. There was an unusual amount of fat, with marked edema of all the tissues. The thymus (fig. 14) was much enlarged. Stumps of thyroid tissue on each lateral aspect of the trachea were still present. No signs of infection or of hemorrhage were evident. The right kidney, normal in size and appearance, lay on the lateral side of the promontory of the sacrum. On micro-

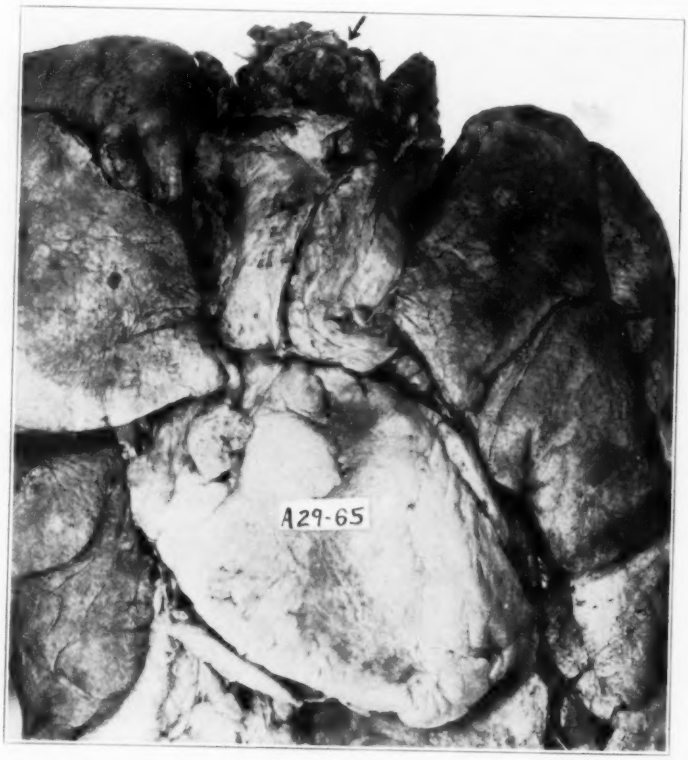

Fig. 14 (case 7).—Anterior view of the thoracic structures. Note the enlarged persistent thymus which has pushed the upper lobes of the lungs apart. The remains of the thyroid are seen above the thymus (arrow).

scopic examination, the thymus consisted of many lymphoid elements, with the persistence of numerous well formed Hassall's corpuscles. Serial sections of several pieces of the enlarged thymus revealed a pea-sized island of accessory thyroid tissue (fig. 15), many of the acini of which were empty while a number of them contained colloid material. Another anomaly observed was the presence of gland tubules, lined by cuboidal epithelium, in juxtaposition with Hassall's corpuscles.

Comment.—It is seen that this patient presented a number of congenital abnormalities; accessory lobes in the right lung, an enlarged persistent thymus, an accessory thyroid embedded in the thymus, retrosternal thyroid and malposition of the right kidney. In addition, there was a familial predisposition to goiter. Experience has shown that congenital defects are often multiple.

Accessory thyroid tissue is most commonly found along the course of the thyroglossal duct, particularly in the region of the hyoid bone

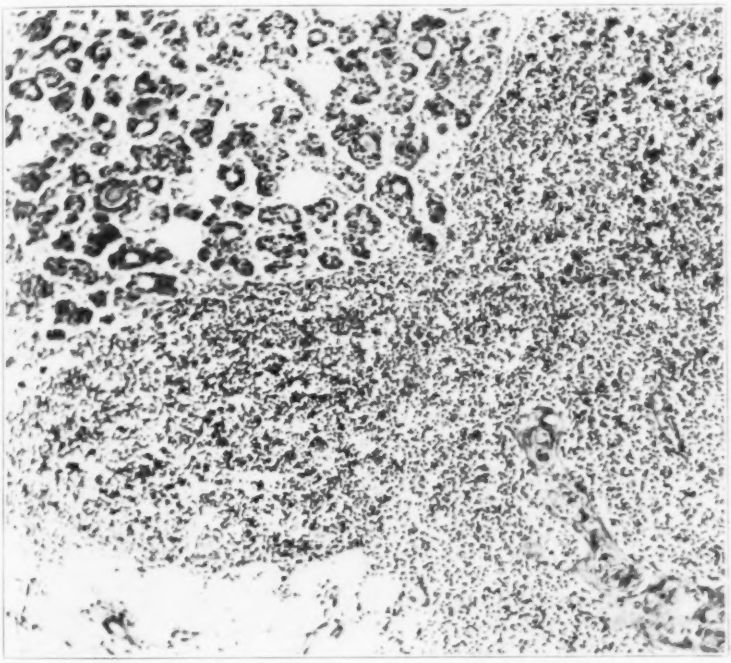

Fig. 15 (case 7).—Photomicrograph of the thymus, showing the island of accessory thyroid tissue at the upper left-hand corner. A number of the thyroid acini contain colloid material. In the lower right corner, there are Hassall's corpuscles. Note the abundance of small thymic cells. Hematoxylin and eosin stains; × 135.

(Streckeisen[38]). In the dog, they are frequently found along the aorta where they may undergo goitrous enlargement, as shown by

38. Streckeisen, A.: Beiträge zur Morphologie der Schilddrüse, Virchows Arch. f. path. Anat. **103**:131 and 215, 1886.

Wölfer.[39] Huttyra [40] was able to demonstrate thyroid tissue even in the heart muscle. In this case, accessory thyroid tissue was found embedded in the substance of the enlarged persistent thymus.

Thyroid tissue has also been found beneath the mucosa of the larynx or the trachea, with or without connection with the main thyroid gland lying outside. These have been found accidentally at autopsy or may have become evident through goitrous enlargements or even through carcinomatous transformation (Cappon,[41] Wegelin [42] and others). Krönlein [43] reported an unusual case of struma intrathoracica retrotrachealis in which the almost fist-sized struma extended down from the inferior pole of the left lobe of the thyroid into the thorax to the tracheal bifurcation between the trachea and esophagus. It markedly compressed the adjacent structures and even produced a marked scoliotic curvature of the dorsal spinal column. In Bevan's two cases [44] of mediastinal tumor, which proved to be substernal thyroid enlargement at operation, the symptomatology was mainly referable to the increased mediastinal pressure. In this case, in spite of the presence of a retrosternal adenomatous goiter and an enlarged persistent thymus, the symptoms were typically those of thyrotoxicosis. The diagnosis of retrosernal thyroid becomes difficult when no toxic symptoms are present. The absence of the thyroid gland in its usual position in the neck, as in Bevan's second case, may serve to put the observer on his guard.

Quiescent retrosternal strumas can be diagnosed roentgenologically if calcium becomes deposited in degenerating, cystic, adenomatous goiters. This was shown in one of our recent cases, in which roentgen examination revealed a large calcified oval ball representing the retrosternal struma, which was later verified at autopsy (fig. 16).

CASE 8.—*Saccular Aneurysm of the Ascending and Transverse Portions of the Aorta Simulating Mediastinal Tumor of Nonvascular Origin.*

J. McC., a white man, aged 43, American, married, a bookbinder, entered the medical service of Dr. Thomas Ordway on Jan. 25, 1928, complaining of cough, shortness of breath and loss of weight.

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39. Wölfer, A.: Die Aortendrüse und der Aortenkropf, Wien. med. Wchnschr. **29**:198, 1879.

40. Huttyra, quoted by von Eiselsberg, A. F.: Die Krankheiten der Schilddrüse, Stuttgart, Ferdinand Enke, 1901, p. 38.

41. Cappon, R.: Versprengte Schilddrüsenkeime in den oberen Luftwegen, Inaug. Dissert., Berlin, Aug. 14, 1911.

42. Wegelin, C.: Zur Genese der intralaryngotrachealen Struma, Centralbl. f. allg. Path. **33**:73, 1922-1923.

43. Krönlein: Ueber Struma intrathoracica retrotrachealis, Deutsche Ztschr. f. Chir. **20**:93, 1884.

44. Bevan, A. D.: Two Cases of Mediastinal Tumor Which Proved to Be Substernal Thyroid Enlargements, S. Clin. North America **1**:957, 1921.

Except for mumps and "rheumatic" pains on one occasion when a child, he had always been in good health. His family history was irrelevant. His wife had had four children and no miscarriages. Their oldest child had died a year previously with Pott's disease.

His present illness was of about four or five months' duration when he entered the hospital. It began with excessive coughing which gradually became worse. The coughing came in paroxysms, especially when he lay down, associated with pains in his chest and profuse perspiration. He noticed that he was becoming weaker and unable to carry on his usual amount of work. Dyspnea occurred on the slightest exertion. Anorexia was marked, and recently he had noticed difficulty in swallowing, the food seeming to stick in his throat. He expectorated a considerable amount of frothy fluid but never any blood.

Fig. 16.—Roentgenogram of a patient admitted in a hypoglycemic semicoma. He had suffered from dyspnea and "asthma," with edema of the ankles, for twenty years. This plate revealed a large ovoid calcified tumor mass, 8.5 by 6.3 cm. (arrow), near the left apical region, suggesting a retrosternal thyroid verified later by autopsy. The trachea is deflected toward the right.

Examination showed a poorly nourished man who had great difficulty in breathing. In his paroxysms of coughing, his face and neck became flushed from the distended blood vessels. A respiratory stridor was evident when one stood near the patient. The lips and mucous membranes were cyanotic. The teeth were in poor condition. The tonsils and pharynx were injected, and some exudate was present. No cervical or suprasternal lymph nodes were palpable. The thyroid was not enlarged.

The superficial veins of the neck and the chest were prominent, owing to the great distention. Expansion was equal on both sides of the chest. An inspiratory

and expiratory thrill could be felt everywhere over the chest. The heart was not enlarged to percussion. The heart sounds were not readily audible, owing to the loud respiratory stridor. The left lung was resonant throughout. There was an area of dulness anteriorly over the right lung, extending from the apex to the third interspace and from the axilla to the sternum. Posteriorly, this area of dulness extended down to the sixth interspace and from the vertebral column to the axilla. Over both lungs, the breath sounds were replaced by a loud inspiratory and expiratory stridor, most marked in the dull areas. No râles were present. The results of the remainder of the physical examination were of no interest.

The temperature ranged between 97 and 98.6 F. The pulse rate averaged 100 and the respirations about 25 per minute. Examination of the blood showed: hemoglobin, 90 per cent; red blood cells, 4,990,000, and white cells, 13,400. Urinalysis and blood chemistry gave normal results. The sputum contained acid-fast bacilli. The serologic test gave a four plus fixation of complement with both

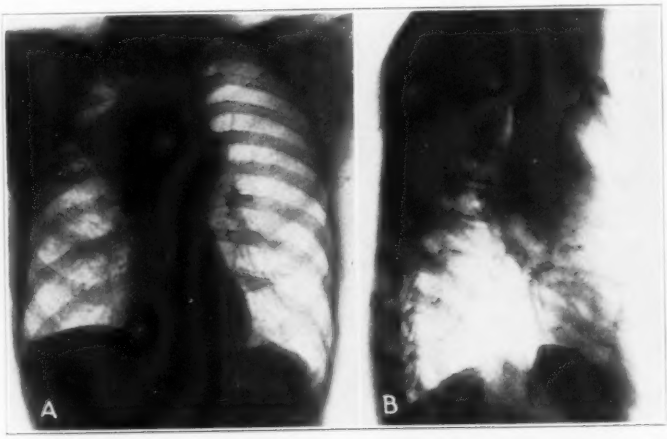

Fig. 17 (case 8).—*A*, the barium-filled esophagus is displaced toward the left. The dense superior mediastinal shadow extends from the first rib to the upper border of the fourth rib anteriorly and 6 cm. to the right of the sternum. *B*, right lateral view. The barium-filled esophagus is constricted at the level of the third rib anteriorly.

the cholesterinized and the acetone-insoluble antigens. The Kahn test also showed four plus.

Roentgen examination showed a dense shadow in the mediastinum extending from the first to the upper border of the fourth rib anteriorly and 6 cm. to the right of the sternum, with compression of the lung tissue at the right upper lobe (fig. 17). On fluoroscopic examination, the esophagus was displaced to the left and constricted at the level of the third rib anteriorly. The whole of the esophagus was smooth and regular. The liquid barium passed down without difficulty although a small-sized capsule was arrested at the level of the third rib anteriorly. The posterior mediastinum was encroached on by the mass, but the vertebrae were intact. On stereoscopic examination, the mass previously described was seen in the anterior mediastinum. There was obliteration of the right diaphragmatic sulcus, suggesting thickened pleura or a small effusion.

The patient rapidly grew weak, and marked dyspnea developed. He died eight days after admission to the hospital.

Autopsy was performed nine hours post mortem. The clinical diagnosis was pulmonary tuberculosis, mediastinal tumor and syphilis. The right pleural cavity was obliterated by dense fibrous adhesions. There were only a few firm adhesions in the left pleural cavity. Both lungs showed active tuberculosis with cavitation.

A saccular aneurysm, nearly 10 cm. in diameter, was found about 4 cm. above the aortic cusps. It included the upper ascending and transverse portions of the aorta. The cavity, about 8 cm. in depth, had a roughened and somewhat stretched-out wall, which was lined by laminated layers of compact thrombus material, partially filling the aneurysmal sac. In many places the aneurysmal wall showed organization of the thrombus. Microscopic examination showed a typical syphilitic mesaortitis with marked atheroma and aneurysmal thinning of the wall.

Comment.—Aneurysms of the thoracic aorta may present diagnostic difficulties. They may be mistaken for tumors, and vice versa. In this case, although both the Wassermann and Kahn tests gave a four plus reaction, there were no tracheal tug, no anisocoria and no inequality in the radial pulse. Fluoroscopic examination showed no expansile pulsation of the mediastinal mass which stereoscopic study revealed to be located in the anterior mediastinum. The symptoms and signs were mainly those of pressure on the trachea, on the superior vena cava and later on the esophagus. Aneurysms generally affect the arterial circulation more than the venous, whereas in this case there was cyanosis of the mucous membranes with marked distention of the superficial veins of the neck and chest. The rapid progress (in from four to five months), cachexia and rapid loss of weight all speak for a malignant condition but the rapidity of the course may have been due to the active pulmonary tuberculosis. As pointed out by Jack and Teacher,[45] their case of mediastinal tumor (endothelioma) with definite expansile pulsation shows that rare as the exceptions may be, there is no medical axiom of universal application.

SUMMARY

1. Eight cases of different types of mediastinal tumor masses are reported.

2. There is not a single pathognomonic symptom or sign on which one can place absolute trust in the differential diagnosis of mediastinal tumors.

3. Metastasis to the central nervous system is commonly observed. Such metastasis may initiate and dominate the symptomatology. Hence, a diagnosis of primary tumor of the brain may be made in these cases.

45. Jack, W. R., and Teacher, J. H.: Case of Mediastinal Tumor with Expansile Pulsation, Glasgow M. J. **87**:84, 1917.

4. Tuberculosis may be suspected in the very early stages because of the persistent cough due to bronchial irritation by the growing tumor mass.

5. Clinical observations must be correlated with the roentgen and laboratory data. Confirmatory evidence is obtained by (*a*) examination of the sputum or pleural fluid for tumor cells, (*b*) examination of the specimen obtained by probatory puncture or through the bronchoscope and (*c*) examination of the superficial lymph nodes containing the metastasis (biopsy).

The clinical histories of the cases reported were used with the permission of Drs. A. W. Elting, T. Ordway, G. E. Beilby, L. W. Gorham and A. H. Stein, and the roentgenograms were furnished by Dr. W. P. Howard.

INFLUENCE OF VELOCITY ON THE RESPONSE TO INTRAVENOUS INJECTIONS*

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I. UNTOWARD EFFECTS OF RAPID INJECTION ("SPEED SHOCK")

The rapid intravenous introduction of pharmacologically active or inert chemicals, drugs and biologic fluids may frequently give rise to immediate and far-reaching nonspecific sequelae, at times serious, and occasionally fatal.[1] This "speed shock" is a hazard to the clinician and annoys and baffles the laboratory worker (charts 1, 2, 3, 4 and 5). In this article we shall describe, localize and discuss the possible mechanism of the deleterious effects of the rapid introduction into the blood stream of relatively innocuous substances.

MATERIAL AND TECHNIC

Our observations were made on anesthetized and unanesthetized animals. For the work without anesthesia, dogs and rabbits were used, and the injections were made with the hand syringe. The rate of injection could not be accurately mea-

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* From the Department of Pharmacology, College of Physicians and Surgeons, Columbia University.

1. Hanzlik, P. J., and Karsner, H. T.: Comparison of Prophylactic Effects of Atropine and Epinephrine in Anaphylactic Shock and Anaphylactoid Phenomena from Various Colloids and Arsphenamine, J. Pharmacol. & Exper. Therap. **14**:425 (Jan.) 1920. Manwaring, W. H.; Brill, S., and Boyd, W. H.: Hepatic Reactions in Anaphylaxis: Hepatic Mechanical Factor in Peptone Shock, J. Immunol. **8**:121 (March) 1923. Dale, H. H.: Histamin Shock, J. Physiol. **41**:318 (April) 1910; **52**:355 (March) 1919; **52**:361 (March) 1919. Manwaring, W. H., et al.: Hepatic Reactions in Anaphylaxis: Hepatic Anaphylatoxin, J. Immunol. **10**:575 (May) 1925. Osborne, T.: Principles of Therapeutics, Philadelphia, W. B. Saunders Company, 1921. Lewis, J.: Route and Rate of Absorption of Subcutaneously Injected Serum in Relation to Occurrence of Death After Injection of Antitoxic Horse Serum, J. A. M. A. **76**:1342 (May 14) 1921. Hanzlik, P. J.: Basis of Allergic Phenomena, J. A. M. A. **82**:2001 (June 21) 1924. Karsner, H. T.: Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, p. 966, with full bibliography. Hanzlik, P. J., and Karsner, H. T.: Anaphylactoid Phenomena from Various Agents Injected Intravenously, J. Pharmacol. & Exper. Therap. **14**:379 (Jan.) 1920; **23**:173 (April) 1924. Hanzlik, P. J.; De Eds, F., and Tainter, M. L.: Blood and Symptomatic Changes Following Intravenous Injections of a Variety of Agents and Solutions, Arch. Int. Med. **36**:447 (Oct.) 1925.

sured, but usually from 2 to 5 cc. was introduced as rapidly as the plunger could be pressed. Under anesthesia, sixty-two animals (dogs, cats, rabbits and monkeys) were used. The dogs were given morphine before anesthesia. The cats, of course, received no morphine. Either a fixed anesthetic (chloretone or sodium isoamyl-ethyl barbituric acid) or ether was administered. In the anesthetized animals, we recorded the blood pressure from the carotid artery, and at times the respirations. Myocardiograms were also made in three of the animals (chart 12). Fluids were injected into the saphenous vein previously prepared with a cannula. When less than 5 cc. was employed, the hand syringe was used and the plunger was driven home as rapidly as possible. Larger injections were made by attaching the cannula to a 25 cc. buret. The fluid was permitted to run in by gravity as rapidly as it might (usually from 3 to 10 cc. per minute). Except when especially mentioned in experiments planned to show the effects of the temperature of the fluids (charts 11 and 12), all the substances were introduced at room temperature.

Substances Introduced.—The substances injected during the course of these experiments included:

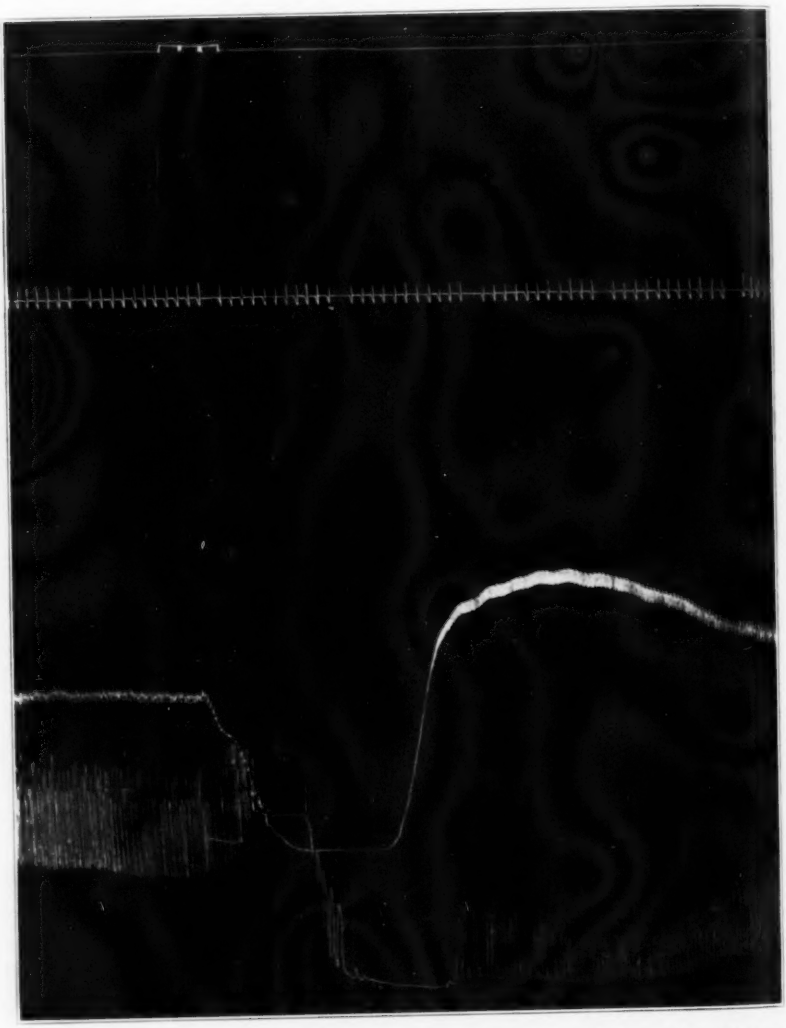
(1) Hypotonic solutions	0.1% sodium chloride
(2) Isotonic solutions	0.9% sodium chloride
(3) Hypertonic solutions	10% sodium chloride
	40% hexamethylenamine
	20% sodium citrate
	50% sodium salicylate
	10% sodium salicylate
	9% calcium chloride
	21% sodium iodide
	9% sodium bicarbonate
	5% copper sulphate
(4) Sugars	5% dextrose
(5) Colloids and gels	50% dextrose
	6% acacia
	25% acacia
	5% gelatin
	10% peptone
	0.1% agar
(6) Suspensions	0.1% Fuller's earth
(7) Drugs (in addition to the aforementioned under hypertonic solutions), caffeine, digitalis, pituitary, nitrites, epinephrine, digifolin, digitan, histamine, strophanthin, arsphenamine, ergot, ouabain, aconitine, coramin, homocamfin, atropine and quinine.	
(8) Biologic fluids	Blood
	Serum

Plan of Experiments.—In general, after waiting for the recovery of the animal from the operative procedure, we obtained a "speed shock" by rapidly introducing 1 or 2 cc. of the agent under investigation (charts 1, 2, 4, 5 and 3). Occasionally, the reaction was fatal (charts 4, 5 and 3). No effort was made to resuscitate the animal. If the animal recovered spontaneously (charts 1 and 2), a slow infusion of a large amount of the same substance was introduced to eliminate the possibility that the reaction obtained might be specific to the substance or to an impurity. The shock was then reinduced by a rapid injection so that we might be convinced that the animal was still "shockable." After recovery, a second and

sometimes a third substance was injected into the animal in a similar manner, and usually, if the animal survived and was still in fair condition (which was often the case), one or more of the drugs of group 7 was employed. Each substance was tried on at least three different animals and was always used at least once on a fresh animal. In a few of the experiments we reversed the procedure and started with a slow infusion and produced shock by a subsequent rapid injection (chart 3).

CLINICAL SYMPTOMATOLOGY OF "SPEED SHOCK"

In all of our animals, irrespective of the nature of the substance injected, irrespective of the type of experiment and of all other controlled variables, we were able at one time or another to elicit in whole or in part a clinical syndrome to which we shall refer as "speed shock." The reactions occurred within from forty to sixty seconds of the injection. These included salivation, vomiting, diarrhea, dyspnea, muscle atony, or at times muscle spasm. Inconsistency and inconstancy of these symptoms was the rule. In fact, this irregularity led us to the belief that some nonspecific variable, probably velocity, was at the bottom of our inability to work out the toxicity and pharmacology of a group of pigments that we chanced to have under investigation. The major symptoms of "speed shock" consisted in changes in the blood and in circulatory and respiratory symptoms. The blood was rendered noncoagulable. We were inclined to the belief that the shock reaction preceded the blood change, and that the latter was indeed but a symptom of the former. In "speed shock," the blood pressure fell precipitously. This might be fatal (charts 3, 4 and 5), or recovery might speedily ensue (charts 1 and 2), so that the tracing at least appeared no different from the preceding strip. Coincident with the circulatory symptoms occurred respiratory distress (charts 1 and 2). There were simple dyspnea or apnea and at times collapse of the lung with a sucking in of the thoracic wall or at other times severe bronchospasm with a ballooning of the chest. Death might result from the respiratory or the circulatory accident. At autopsies, the most marked changes were usually found in the lungs, confirming the clinical observations, there was either atelectasis or emphysema. Often large fresh thrombi could be found in the pulmonary veins. Frequently multiple punctate hemorrhages were noted in the abdominal viscera. Less tempestuous fluctuations in blood pressure were also produced by altering the rate of flow within narrower limits (charts 9 and 10). An infusion made slightly too fast often caused a gentle but continuous fall of blood pressure which adjusted itself when the infusion was stopped or slowed. This reaction is probably similar in every way, except quantitatively, to the "speed shock."



Charts 1 and 2.—"Speed shocks" with 20 per cent sodium citrate and spontaneous recovery. Note the fall of blood pressure (upper tracing) and two types of respiratory response (lower tracing), the one with cessation in expiration (bronchospasm with emphysema) and the other in inspiration (collapse). The time marker is in periods of five seconds in all charts.

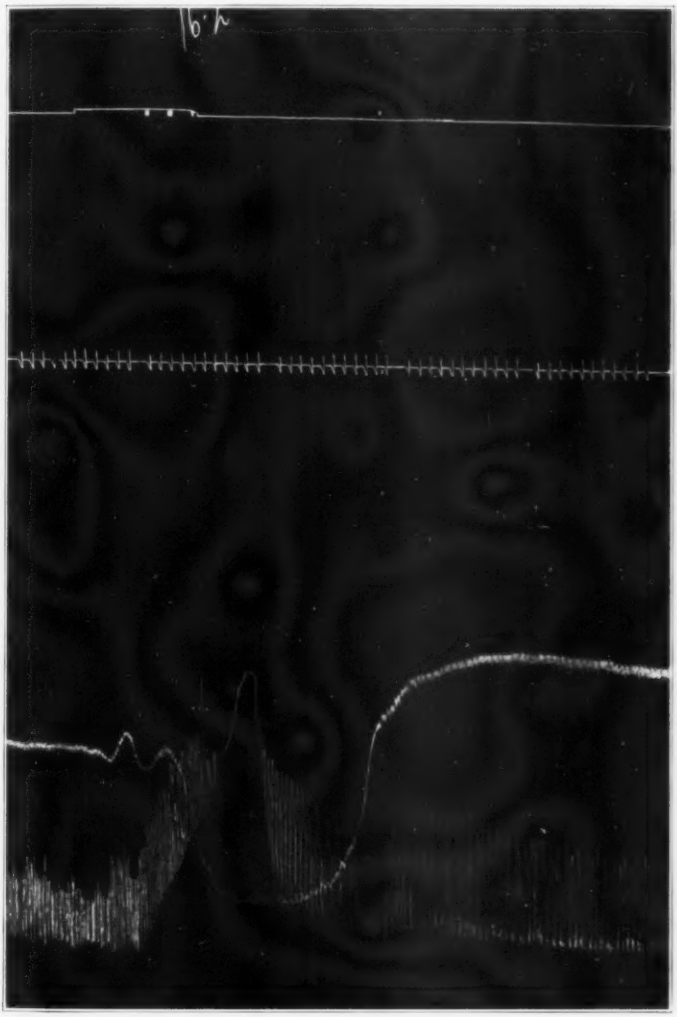


Chart 2.

FACTORS THAT MODIFY "SPEED SHOCK"

The "speed shock" could not be consistently obtained with all of the substances. If an injection of 1 or 2 cc. was not successful, usually a slightly greater amount of fluid (up to 5 cc.) or an increase in the velocity of injection produced shock (chart 6). This was true whether we are using a comparatively inert and small molecule such as sodium

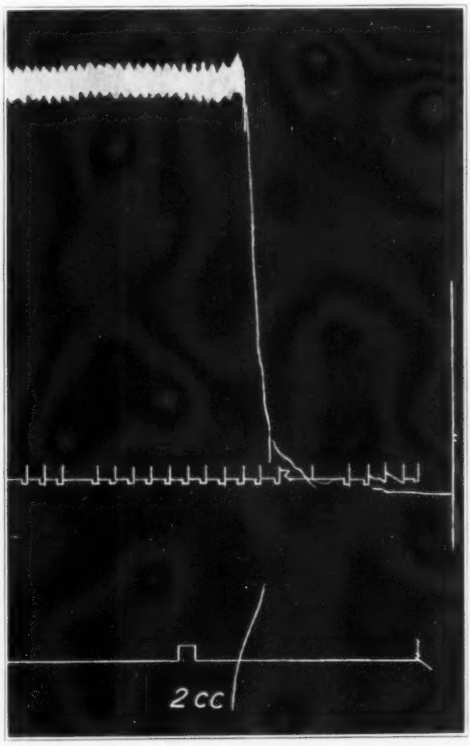


Chart 3.—"Speed shock" with hypotonic solution (0.1 per cent sodium chloride). Previously the animal had received 25 cc. of the same solution slowly (1 cc. per minute) without any effect on the blood pressure. This illustrates how much more important is velocity than concentration, size of molecule, etc.

chloride (chart 3) or a complex molecule such as melanin (charts 4 and 5). Using 1 or at most 2 cc., we could obtain a shock regularly with 20 per cent sodium citrate (charts 1 and 2) or 10 per cent sodium chloride. In general, it was easier to produce shock with the hypertonic solutions, and a large molecule was more effective than

a small one. Again, the shock seemed more readily produced with a fluid than with a viscous substance such as acacia (chart 14). The 6 per cent acacia produced shock more easily than the 25 per cent solution, despite the large number of molecules in the latter. Unfortunately, we had no way of measuring these quantitative differences. The influence of the temperature of the fluids will be discussed later.

REPEATED SHOCKS AND PROTECTION

Repeated shocks were produced with all of the substances mentioned except the sodium bicarbonate and the calcium salt (charts 6 and 12). In some cases it seemed that there was a short period in which the animal was not shockable. A certain amount of protection also seemed to occur with acacia (chart 14), and we had difficulty in producing shock by injecting into one saphenous vein while an infusion of acacia was running into the other vein.

IMPORTANCE OF OTHER VARIABLES

The production of the shock picture with so variable a list of substances pointed to the fact that the reaction must be due to some constantly present variable. Consequently, it was necessary to evaluate the importance of all other possible contributing nonspecific factors.

1. Species idiosyncrasy was excluded, as cats, dogs, rabbits and monkeys were used. We might add, prematurely, that identical reactions occur in man.

2. Morphine as a contributing cause was excluded, as it was not used in cats.

3. Anesthesia and anesthetics were unimportant, for we obtained the syndrome in unanesthetized animals, and in animals anesthetized with ether or with fixed anesthetics.

4. Pyrogenic substances in our laboratory diluents were excluded, for the reaction was not obtained when slow infusions were used (chart 6). Many of the agents were purchased in ampules in the open market.

5. The state of the circulatory system was unimportant. Shock could be produced equally well whether the blood pressure was at a normal or a subnormal level (chart 13).

6. The bulk of fluid injected (frequently very large) modified but did not appreciably affect the reaction. At times, with colossal amounts of fluid, such as from 10 to 20 cc. per kilogram, we observed "bulk reaction." It consisted usually of a slight rise of blood pressure, a

considerable increase in the fling (pulse pressure) and some slowing in the rate of the heart.

7. The temperature of the injected fluid played a minor and relatively unimportant rôle (charts 11 and 12). Usually the fluids were injected at room temperature. In certain of the experiments the temperature of the fluids was carefully controlled. Shock was obtained at one time or another with any given substance at any temperature whether chilled or warmed to body heat. The reaction was slightly more severe perhaps when the solution was cooled or chilled. The

Charts 4 and 5.—"Speed shock" with a complicated molecule. Fatal reaction occurred with 4 cc. containing 100 mg. of "melanin" given in ninety seconds (2.7 cc. per minute).

thermal effect, however, was slight and insignificant when compared with velocity. Also, chilled solutions could be injected with impunity provided only that the rate of injection was controlled.

8. The production of protein split products, such as histamine, was investigated by subjecting the fluid to dialysis. The dialysates reacted exactly as the whole products or residue in the bags.

9. Concentration was excluded by obtaining shock with hypotonic solutions (0.1 per cent sodium chloride) as well as more concentrated solutions (chart 3).

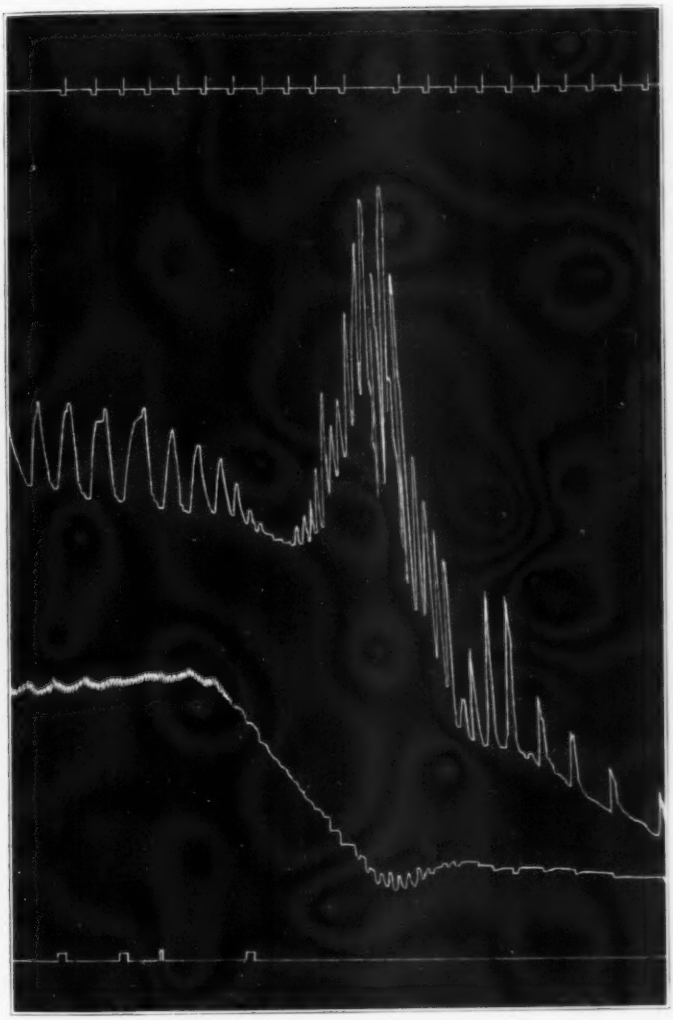


Chart 5.

10. Specific effects of the agents employed could be excluded by the irregularity of results and by the harmlessness of huge slow infusions of the agent.

The speed reaction that we have described is a definite phenomenon. It has previously come to the attention of other workers. Sollmann [2] wrote of "a primary fall in blood pressure which is apt to occur with all kinds of intravenous injections and which has been an annoying complication of experimenters on animals and no less annoying in clinical practice." In their complete report on the studies of intravenous

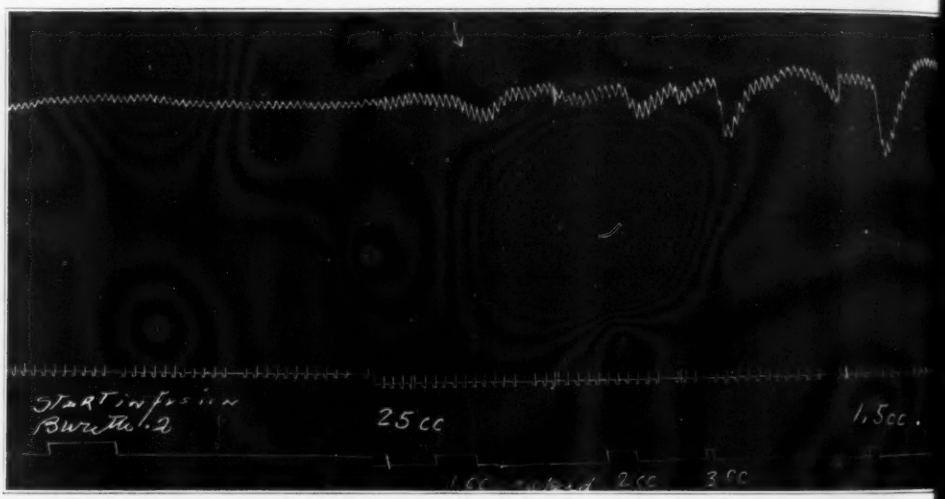


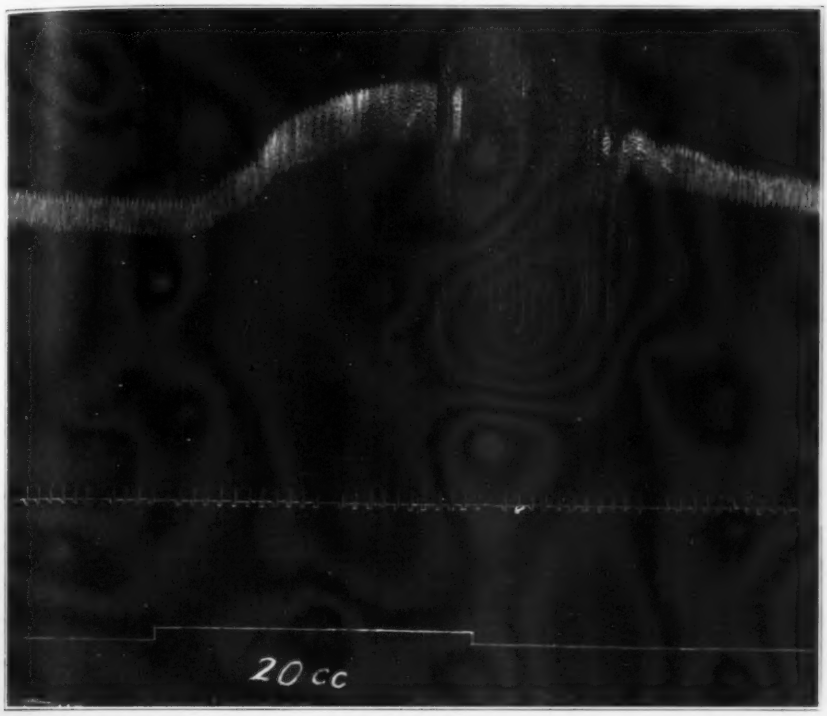
Chart 6.—Between the first and second strips fifty minutes elapsed, during which time a continuous slow intravenous drip of Witte peptone (10 per cent) was administered. A total of 25 Gm. in 25 cc. was infused or 12.5 cc. per kilogram of body weight or 1.25 Gm. per kilogram at a rate of 1 cc. per two minutes. No changes were noted until later slight shocks were obtained with 1 and 2 cc. injected rapidly and marked shocks with 3 and 2.5 cc. This illustrates protection by slow drip, toxicity due to speed, ability to cause shock repeatedly and absence of protection.

injections, the Commission appointed by the Council on Pharmacy of the American Medical Association [3] said:

"The rapid administration introduces several hazards: (1) the danger of overwhelming the heart and circulation with too great a

2. Sollmann, T.: Manual of Pharmacology, ed. 3, Philadelphia, W. B. Saunders Company, 1927, p. 73.

3. Hunt, R.; McCann, W.; Rowntree, L.; Voegtlin, C., and Eggleston, C.: Status of Intravenous Therapy, J. A. M. A. **88**:1798 (June 4) 1927; **90**:764 (March 10) 1928; **91**:1372 (Nov. 3) 1928; **92**:2099 (June 22) 1929.



Charts 7 and 8.—Bulk reactions from 6 and 25 per cent acacia. Note the slight effect on the systolic but the considerable fall of diastolic pressure and the increase of pulse pressure. Compare with "speed shock."

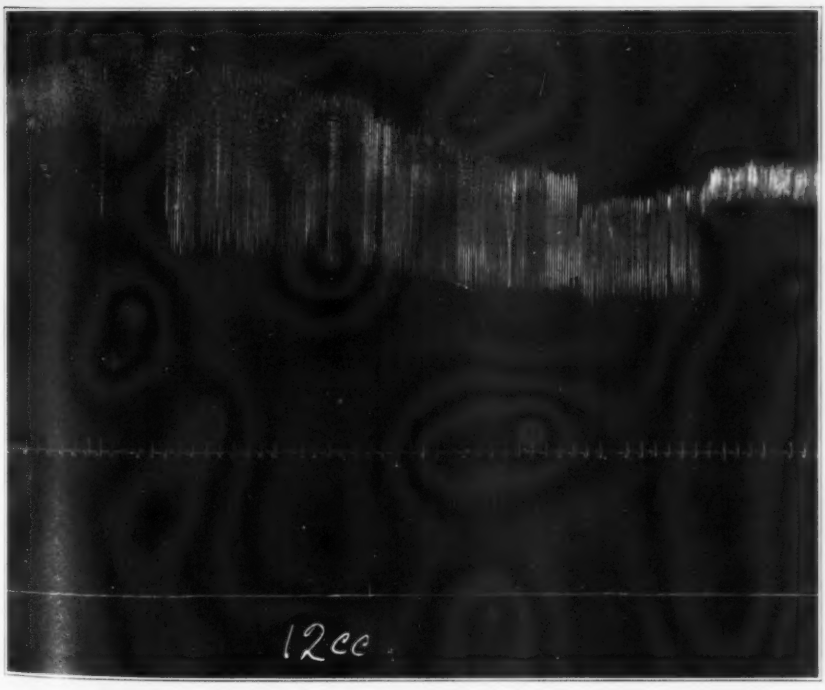
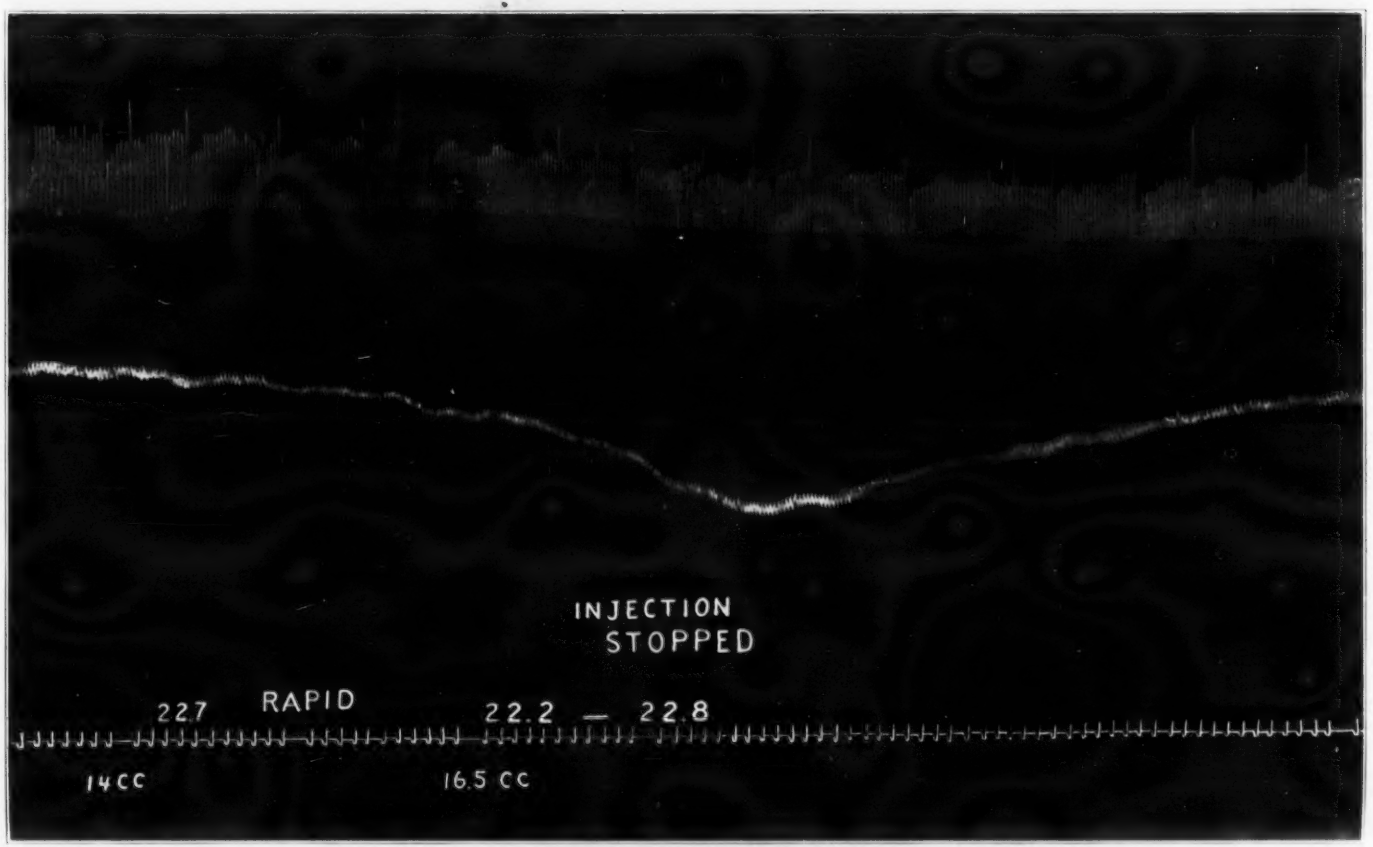


Chart 8.



Charts 9 and 10.—Less violent speed reactions due to narrow fluctuations in the velocity of injection. In chart 9, sodium chloride (10 per cent) infused at a rate of 1 cc. per minute caused slight lowering of blood pressure (lower tracing). The respirations (upper tracing) were unchanged. After injection was stopped and recovery followed. In chart 10, recovery followed when the rate of 2 cc. per minute was cut down. Compare also

volume of fluid, and (2) the risk of breaking down some compensatory mechanisms as those which maintain the reaction of the blood, its osmotic tension, viscosity, and the like, within the narrow limits of normality and the likelihood of carrying the drug in too high concentration."

The first statement obviously refers to what we have described as the "bulk reaction." This, we believe, is overemphasized, and in our experience was not particularly harmful. The second statement emphasizes the rôle of concentration, and this, too, we believe, is relatively unimportant as compared with the rapidity with which the molecules and agents are introduced into the blood stream.

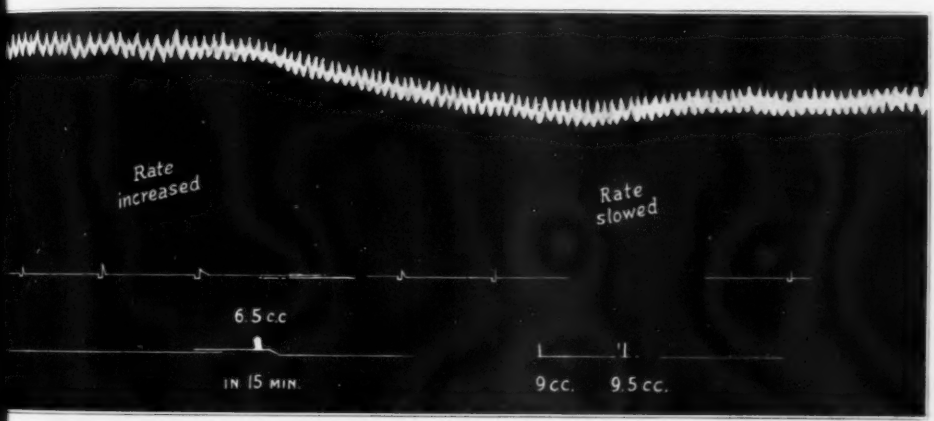


Chart 10.

Further on this Committee stated that when "one considers the nicety with which these balances—physiological and physicochemical—must be preserved, the grave consequence of their disturbance and the relative ease with which they may be upset, it is truly remarkable that there are not many more serious accidents than seem to be the case."

These statements all apparently arise from a familiarity with the "speed shock" that we have described and that these other investigators apparently encountered but did not interpret. Even in his very complete textbook on pharmacology, and particularly in the section on "factors which modify intravenous injections," Sollmann [4] did not mention velocity. The other textbooks on pharmacology are similarly silent on this point.

4. Sollmann (footnote 2, p. 82).

LOCALIZATION OF THE SITE OF "SPEED SHOCK"

The localization of the site of the production of the reaction was our next concern. At one time we were of the opinion that (*a*) some acute chemical disturbance occurred either in the hydrogen ion concentration or of the anions and cations of the blood. Loeb,[5] who has studied this problem, looked over our work and assured us that the speed with which this reaction was experienced eliminated the possibility that the disturbance was in these spheres and dissuaded us from any chemical studies. This seemed particularly reasonable, because we obtained the

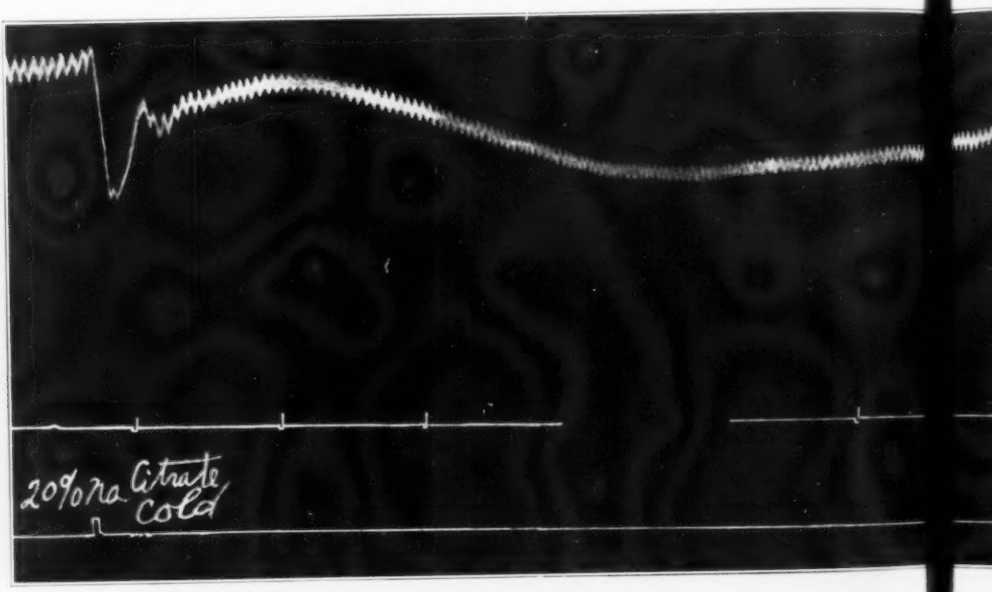


Chart 11—Left

Charts 11 and 12.—Thermal experiments. Note the shocks recorded when the same solution, chilled, cooled and at body temperature was used. Note in one experiment that shock was obtained with blood pressure at 30 mm. of mercury, showing that the condition of the circulation is not a factor. Compare the shock

shock with any of the anions or cations and irrespective of the reaction of the fluids. The appearance of the trace suggested also (*b*) the intervention of the vagal system (chart 3). However, the reaction could be

5. Atchley, D. W.; Loeb, R.; Benedict, R., and Palmer, W. W.: Physical and Chemical Studies of Human Blood Serum, Arch. Int. Med. **31**:606, 611 and 616 (April) 1923.

obtained with the vagus intact or severed, and it could neither be prevented nor be modified in any way by full doses of atropine. (*c*) Cardiac collapse was excluded by the myocardiograms which showed slight or secondary changes in the auricle and less in the ventricle (chart 12). The incoagulability of the blood suggested to Dr. Loeb that we might here be dealing with (*d*) a functional hepatic damage, and it was at his suggestion that we tried hepatic exclusions (chart 13). We could not produce the velocity reaction in animals when there had been a complete removal of the liver.[6]

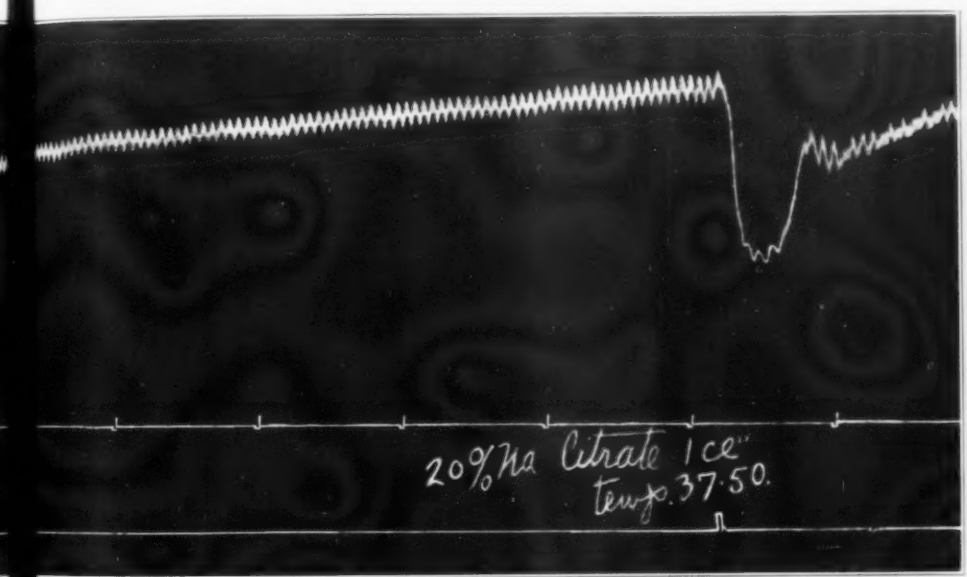


Chart 11—Right

picture with the histamine reaction, especially in chart 12 in which a simultaneous myocardiogram was made (upper tracing, auricle; middle tracing, ventricle; lower tracing, blood pressure). The changes in the heart followed the fall of pressure and were more marked in the auricle than in the ventricle. The reaction is not central in origin.

POSSIBLE MECHANISM

Obviously, then, the disturbances that we have described cannot occur without the intervention of the liver cell. The rapidity of its development, for it followed the injection very regularly between from forty to fifty seconds, suggested that some toxic substance of the histamine[7]

6. Manwaring et al. (footnote 1, fourth reference).

7. Dale (footnote 1, third reference).

B.P. 30
BP 30
15% NaCl
0.5cc
0.9% NaCl
Cold
2cc
10% NaCl
40
2cc
0.9%
NaCl
2cc
Cold
Tab Histamine
0.5mg

Chart 12

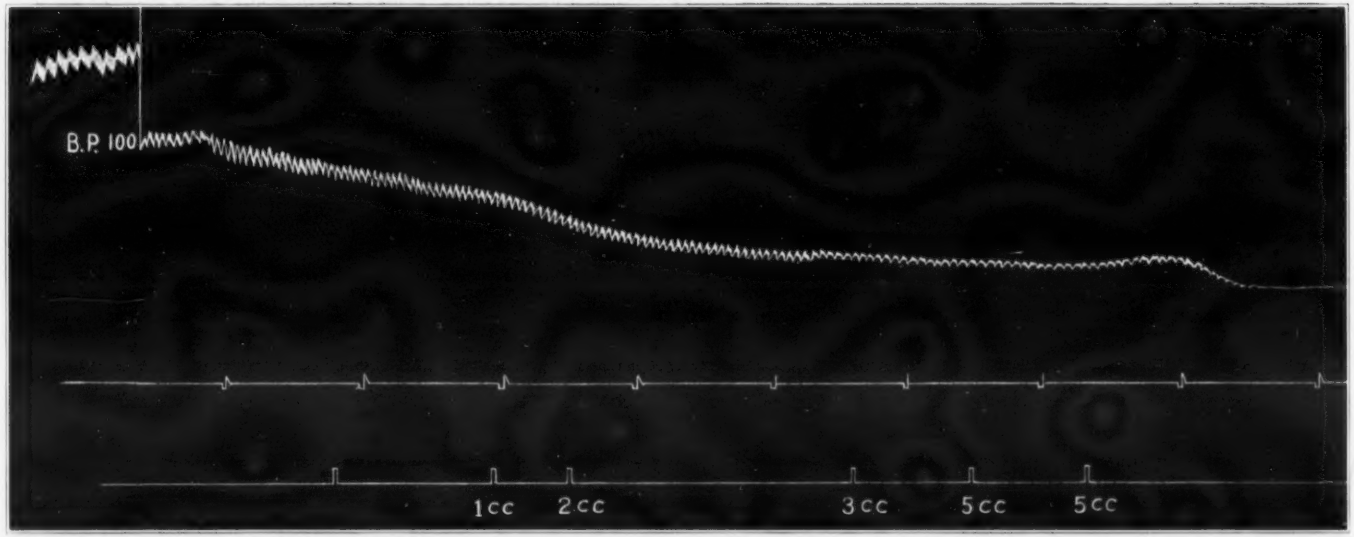


Chart 13.—Complete extirpation of the liver in a dog weighing 16 Kg. The pressure was 100 at the end of the operation and fell progressively during the experiment. Shock could not be obtained with 1, 2, 3, 4 and 5 and again 5 cc. of sodium chloride (10 per cent). Compare with chart 9, where shock could be obtained with pressure at 30.

present with the substance that produces true[8] anaphylaxis. It too is not demonstrable in the peripheral blood though present in the blood from the ligated inferior vena cava. It is our belief that the site of action of the "speed shock" is in the liver cell. The damage to the cell obviously occurs from a physical cause—a rapid collision of molecules irrespective of their configuration or chemistry. As a result of the temporary cell damage, some potent and labile substance is liberated or escapes destruction by the liver, and this substance is responsible for the symptoms described. The toxic substance must be readily destroyed and readily formed anew. Whether or not it is histamine is a problem beyond our capabilities.

RELATIONSHIP BETWEEN "SPEED SHOCK" AND SOME SIMILAR BIOLOGIC PHENOMENA

Reaction pictures resembling "speed shock" are frequently described in the literature. A great variety of names has been applied to related if not identical phenomena: colloidoclasis, hemoclasis, anaphylactoid phenomena, etc. It is our opinion that all of these have in common an injury to the liver cell. We wish to discuss here the importance of velocity in the production of these related phenomena—particularly the anaphylactoid reaction—to inquire specifically whether or not the speed of injection is the variable at the root of all these reactions. We are reluctant to open up controversial data, but we feel the necessity of emphasizing the importance of velocity and of clearing away the multiplicity of names with their implications.

(1) *Anaphylactoid Reaction.*—Of all these reactions the anaphylactoid phenomena have been most completely and painstakingly studied by Hanzlik, Karsner and their associates[8] in a classic series of experiments. These have been summarized individually by Hanzlik[9] and Karsner.[10]

These authors have furnished us with a notably complete picture of symptomatology and the alterations that occur in the chemistry of the blood. Because of the resemblance to anaphylaxis, they coined the term anaphylactoid, and they have pointed out the extreme importance of this reaction in the general field of biology and medicine because of its relationship to true anaphylaxis and other immunologic

8. Hanzlik, Karsner et al. (footnote 1, first, seventh, eighth, ninth and tenth references).

9. Hanzlik (footnote 1, seventh reference).

10. Karsner (footnote 1, eighth reference).

phenomena and its close alliance to such interesting and baffling clinical phenomena as the posttransfusion chill, the nitritoid crises and reactions following the injections of foreign protein into the veins.

They have concluded that[11] the reaction depends on the "nature of the agent used, its dose, concentration and the state of the physical functions of the animal." No mention of velocity is made in any of the articles other than to state that the injections were made through the buret at the rate of 3 cc. per minute. We are of the opinion that velocity was of paramount importance in their work and that the reactions were dependent slightly if at all on the "agent used, its dose, concentration or the state of the physical functions of the animals." They state again that "physical and chemical changes in the blood and tissues may always be expected when agents reach the blood stream in effectual concentration and especially when introduced into the blood stream," whereas we believe this to be true only when the molecules are driven rapidly into the blood stream and untrue when the molecules are slowly introduced ("intravenous drip") even if their concentration be great.

We have taken the liberty of reviewing the articles from our point of view. In the most recent and complete work, fifty-six injections were made into twenty-seven dogs anesthetized with ether.[12] The fluids were warmed and given slowly through the buret. The rate of speed is not mentioned in this article, but in an earlier paper describing work done with guinea-pigs, a rate of 3 cc. per minute was used. According to the charts accompanying this paper, however, the rate of injection seems to have been much more rapid. Measuring from the arrow indicating the start of injection to the fall in blood pressure indicating the reaction, so brief a period elapses that the fluids must have been introduced about as rapidly as was possible. In chart 1,[13] 66 cc. was introduced in slightly more than one minute. In the other six charts the rate seemed almost as rapid.

From the published charts we find that twenty-three injections had no appreciable effect on the blood pressure, pulse or respirations (nos. 12, 13 and 15 with 0.9 per cent sodium chloride; no. 5 with methenamine; nos. 3, 15 and 18 with 10 per cent sodium chloride; nos. 8 and 10 with sucrose; nos. 11, 13 and 15 with dextrose; no. 19 with urea; no. 19 with acacia; no. 20 with gelatin; no. 29 with barium; no. 19 with calcium chloride; no. 19 with sodium bicarbonate; no. 17 with citrate; nos.

11. Hanzlik et al. (footnote 1, seventh and tenth references).

12. Hanzlik et al. (footnote 1, first and tenth references).

13. Hanzlik et al. (footnote 1, tenth reference).

13 and 23 with sodium iodide; nos. 17 and 20 with disodium acid phosphate); in eleven experiments the animal was in such poor condition at the time of injection that no conclusions could be drawn (nos. 21 with tyrode solution; no. 14 with methenamine; no. 16 with urea; no. 21 with sodium chloride; no. 24 with agar; no. 21 with horse serum; no. 28

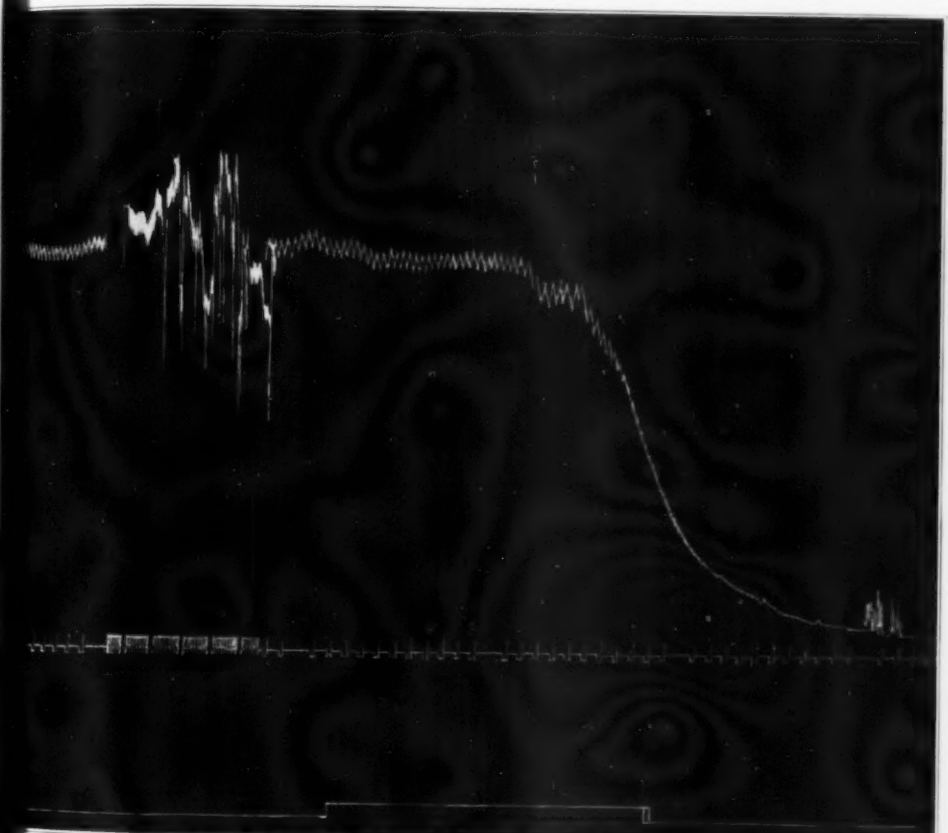


Chart 16.—"Speed shock" from autotransfusion of blood. At 7, 5 cc. of blood was withdrawn from the heart. At 8 the blood was infused rapidly through a buret into the saphenous vein of the same animal. Fatal "speed shock" resulted. At autopsy, the heart was still beating and there was no evidence of bleeding.

with citrate; no. 27 with peptone; no. 16 with sodium bicarbonate, and no. 22 with sodium iodide); in three animals so large a bulk of fluid had been introduced that the reaction seemed to result from volume (no. 17 received 575 cc.; no. 20, 310 cc., and no. 11, 445 cc.). Four animals

collapsed some time after injections, apparently from a specific toxicity of the drug employed (methenamine and sodium salicylate). Fifteen animals experienced immediate reactions of the type that we have described and that these authors termed anaphylactoid (nos. 25 and 26 with agar; no. 14 with sodium chloride; nos. 15 and 16 with methenamine; nos. 18 and 23 with acacia; nos. 28 and 29 with kaolin; no. 18 with calcium chloride; no. 32 with disodium acid phosphate; no. 28 with histamine; no. 28 with peptone; no. 27 with arsphenamine). This summary of these data excludes eleven of fifty-six experiments. Of the remaining forty-five, twenty-three (52 per cent) were negative, three (7 per cent) had a bulk reaction, four (9 per cent) had a late collapse and fifteen (32 per cent) showed the reaction we are now discussing.

Again, if one studies the individual agents employed, the same irregularity is observed. Of four injections of saline, three gave no response and one produced shock; of five with 10 per cent sodium chloride, three produced no response and two caused convulsions; of three with agar, two caused shock and one an elevation of blood pressure; of two with calcium chloride, one produced shock and one no effect. This irregularity, shown in analyses from all points of view, argues strongly against the reactions being caused by the "nature of the agent, its dose, concentration, or the state of the physical functions of the animal." We cannot possibly conceive of an interpretation of the shock reaction as due to the agent introduced, knowing full well that agar, saline, dextrose and acacia are absolutely inert *sui generis*.

The use of the word anaphylactoid, we believe to be misleading. Hanzlik and Karsner have themselves pointed out the differences between true anaphylaxis and the "anaphylactoid" phenomenon. The latter is not necessarily caused by protein; it usually appears only on intravenous injection; there is no period of incubation; there is no true and definite state of protection; hypersensitivity is not transferable, and desensitization does not occur. The sole relationship to anaphylaxis as we interpret it is the fact that both cause a disturbance of the liver cell giving rise secondarily to an identical syndrome. From a biologic and immunologic standpoint the reactions are wholly dissimilar.

Karsner[14] later indicated this when he said, "the resemblance is signified by the term 'anaphylactoid reactions or phenomena' but this does not indicate necessarily that in their essential nature they are directly related to anaphylaxis." Again he[15] stated that "anaphylactoid reactions are for the most part obviously in the circulating fluids

14. Karsner (footnote 1, eighth reference, p. 969).

15. Karsner (footnote 1, eighth reference, p. 988).

operating secondarily on various body mechanisms, whereas the reaction in anaphylaxis is independent of changes in circulating fluids . . . no presentation can overcome the fact that anaphylaxis is an antigen-antibody reaction and that anaphylactoid reactions are not." Hanzlik[16] also stated that "whatever the ultimate explanation of the anaphylactoid reaction, the results of this paper indicate that blood and symptomatic changes occur from agents physically and chemically unrelated, some of which are relatively inert in the ordinary sense and also that more profound changes in the blood can occur than current conceptions of regulator mechanisms would indicate."

In place of the term anaphylactoid, we suggest that this syndrome be called "speed shock." This emphasizes the most potent factor in its pathogenesis, thus being of the utmost practical value, and, by omission, stresses the relative unimportance of the "nature of the agent used, its dosage or concentration." It is thus a reaction based on technical error rather than a pharmacologic, chemical or immunologic entity.

(2) *Relationship to Drug Responses.*—In pharmacologic studies, the "speed shock" might either serve as a constant hazard in any intravenous therapy or it might cloud studies of posology and toxicology.

(*a*) Production of "Speed Shock" by Commoner Drugs Used in Therapeutic Doses: At the end of a number of our experiments, both when animals were in good condition and when they were in a state of simulating shock or collapse, we injected in therapeutic doses many of the more frequently used drugs. These were given as rapidly as possible in an effort to produce the "speed shock." At times, especially with caffeine and the digitalis bodies, a rise of blood pressure was obtained. We succeeded in obtaining typical "speed shocks" with caffeine, digitalis bodies, ergot, atropine, strychnine, quinine, arsphenamine and homocaffeine. The shocks were not regularly produced. These results served to emphasize anew the dangers of intravenous therapy, for especially in clinical emergencies, the clinician might actually produce the "speed shock" in his effort to introduce a therapeutic agent rapidly.

(*b*) Velocity as a Factor in Studies of Posology and Toxicology: Studies of dosage and toxicity should take into account the factor of velocity. To take an extreme example, histamine (chart 15), though a potent vasodepressor in high concentration, when given as slowly as described previously appears to be an inert substance. The opposite error of attributing to a specific drug toxic symptoms resulting from too rapid injection is more frequent. Throughout the work of Hanzlik

16. Hanzlik (footnote 1, tenth reference, p. 503).

and Karsner, previously referred to, "speed shock" symptoms are attributed to the specific agent under consideration. Without wishing to dwell again on these data, we believe that the long list of drugs and chemicals investigated by them are relatively innocuous with the exception of copper sulphate and sodium salicylate. The latter are horribly toxic. This is worthy of emphasis because of the use of sodium salicylate for injection into varicose veins. Among the substances that are quite nontoxic *sui generis*, we wish to stress hypotonic, hypertonic and isotonic saline, sodium citrate, iodide and particularly, acacia. The importance of the absolution of acacia is emphasized by the controversies regarding its use clinically in shock and hemorrhage. Many report exceedingly unfavorable experiences, while others (most recently Keith at the Mayo Clinic [17]) are impressed with its value and have failed to encounter untoward reactions. This controversy might well be settled if the work with acacia is repeated with careful attention to velocity in the injection of the fluids. Our experiences with acacia in the laboratory lead us to believe that it may be an enormously valuable clinical adjuvant. We have found the 25 per cent solution to be less likely to cause "speed shock" than the 6 per cent. We have been able also to produce "speed shock" with arsphenamine. This suggests that there might be an intimate relationship between the nitritoid crises and the "speed shock," if, indeed, these are not found to be identical. Another example of error introduced by "speed shock" is the primary fall of blood pressure resulting immediately following the intravenous administration of digitalis.[18] This has been extensively studied in view of the fact that it is difficult to understand so rapid an effect from a drug that is notoriously deliberate in its dynamics. We are convinced that this is not a specific effect of digitalis, but that it is caused by overrapid introduction of the solution. This observation has extreme clinical significance in the management of emergencies which demand rapid digitalization per vein. "Speed shock" is of great significance, too, in the interpretation of the results of injection of the so-called blood pressure reducing substances, particularly those derived from the liver. Workers in these fields should particularly mention their rate of injection before discussing the specificity of the product under investigation.

(3) *Posttransfusion Reaction.*—We were curious to ascertain whether the reactions following transfusion might be related to the

17. Keith, N. M.: Intravenous Medication, J. A. M. A. **93**:1517 (Nov. 16) 1929.

18. Cohn, A. E., and Levy, R.: Effect of Therapeutic Doses of Digitalis on the Contraction of the Heart Muscle, J. A. M. A. **74**:1597 (June 5) 1920.

"speed shock." In one experiment we withdrew 5 cc. of blood from the heart of an anesthetized animal. The blood pressure and respiration were momentarily affected, and when they were normal again we rapidly infused the blood from a buret. The animal died instantly with the syndrome previously described (chart 16). The present tendency of transfusion specialists is to increase the speed of injection, especially when the syringe method is employed. These studies suggest strongly the necessity of reopening the problem of posttransfusion reactions from the standpoint of consideration of the velocity injection. Our experiences would suggest that slowly administered transfusions of citrated blood might show a complete absence of the velocity reactions, and these could easily be compared with a series of rapid injections.

(4) *Sudden Deaths Following Intravenous Injections.*—In Lamson's[19] report on sudden deaths, he stated that many of the deaths were "anaphylaxis-like phenomena." No mention of velocity is made in these analyses. Similarly, in the report of Drinker and Brittingham[20] concerning two deaths following transfusion, all of the possible factors are analyzed except velocity. We suggest that velocity might be the unknown factor in these fatalities and that the syndrome produced might have been "speed shock."

SUMMARY

1. The rapid injection into the vein of any molecule may result in widespread disturbances.

2. This syndrome is described. The term "speed shock" is suggested.

3. "Speed shock" may terminate fatally.

4. The primary disturbance occurs in the liver cell.

5. The relationship between "speed shock" and the anaphylactoid reaction and other allied biologic phenomena such as the nitritoid crisis, posttransfusion reaction, etc. is discussed. The belief is expressed that these may be dependent on "speed shock." If not, their similarity rests on their common site of origin, viz., the liver cell.

6. "Speed shock" is important to the pharmacologist, and errata due to failure to consider the factor of velocity are illustrated.

7. In addition to its rôle in the foregoing conditions, "speed shock" may be important to the clinician as an explanation of the sudden deaths reported following intravenous injection.

19. Lamson, R. W.: Sudden Death Associated with Injection of Foreign Substances, J. A. M. A. **82**:1091 (April 5) 1924.

20. Drinker, C. K., and Brittingham, H. H.: Transfusion Reactions, Arch. Int. Med. **23**:133 (Feb.) 1919.

II. TOLERANCE TO SLOW INFUSIONS ("THE INTRAVENOUS DRIP")

Laboratory workers and clinicians alike recognize the importance of introducing fluids slowly into the blood stream. Friedmann [21] reported 150 instances of patients treated with what he termed an "intravenous drip" at the rate of about 2 to 5 cc. per minute. Dextrose with added epinephrine was employed. The most enthusiastic and consistent advocate of this type of therapy in this country has been Titus.[22] By means of an ingenious apparatus he infuses intermittently from 50 to 75 Gm. of dextrose in 25 per cent solution at a rate of 4 cc. per minute. He has pointed out its usefulness in toxic conditions associated especially with pregnancy. We have been unable to find any uniformity in the definition of a slow injection. According to the Committee on Intravenous Therapy[3] appointed by the Council of Pharmacy of the American Medical Association, intravenous injections should always be given slowly. They quote only the figures from the workers at the Mayo Clinic, who regard a rate of from 10 to 20 cc. per minute as a slow injection for water, salts and dextrose. Keith [17] regarded from 30 to 40 cc. a minute as a satisfactory rate of injection for dextrose. He mentioned velocity again only to state that the rate of injection of intravenous solutions is often too rapid. In Osborne's textbook on therapeutics[23] an injection of 1 quart in thirty minutes or 30 cc. per minute is called a slow injection. Hanzlik and Karsner[24] advocated 3 cc. per minute in laboratory animals.

MATERIAL AND TECHNIC

In the first section of this paper we have described the materials and methods employed in our present study. Here we shall discuss the results obtained in the same experiments, emphasizing, however, the relative innocuousness of the slow injection (intravenous drip) (charts 6 and 15) rather than the harmful effects of the speed shock (charts 1, 2, 3, 4 and 5).

The slow infusions were made through the buret. Usually a Murphy drip was placed between the tip of the buret and the vein cannula, so that we could accurately regulate the rate of flow. Attempts to use complicated automatic apparatus were early discarded. Conditions that require intravenous administration are of sufficient importance to warrant the constant presence of the experimenter or clinician. There are so many variables, such as the variation in height of the column of fluid, the patency and caliber of the tubing, vein clotting, changes in blood pressure, etc., that no piece of apparatus can be found to care

21. Friedmann, M.: Ueber intravenose Dauerinfusion, München. med. Wchnschr. **60**:1022 (Nov.) 1913.

22. Titus, P.: Apparatus for Regulating Rate of Flow and Temperature of Intravenous Injections of Dextrose and Other Solutions, J. A. M. A. **91**:471 (Aug. 18) 1928.

23. Osborne (footnote 1, fifth reference).

24. Hanzlik and Karsner, in Sollmann (footnote 2, p. 380).

for all the exigencies that arise. We wish to emphasize again that our solutions were injected at room temperature. This was a deliberate measure on our part to accentuate the importance of velocity in the continuous slow injection. The chart appended presents data on the tremendous quantities of fluid bulk and substances that we were able to introduce into the blood stream under these conditions with absolute impunity and without altering the blood pressure. It is in striking contrast to the serious and often fatal reactions that were obtained in using the same substances in small amounts but given rapidly into the blood stream.

MODIFICATION OF CONCEPTION OF SPECIFIC TOXICITY

These figures demand a new definition of "specific toxicity" of substances. The degree to which slow infusion may modify conceptions of toxicity is best illustrated by a remarkable experiment (chart 15) with histamine.[19] Twenty-seven cubic centimeters of histamine (1 per cent)

Effects of Slow Infusions

Experiment	Weight of Animal, Kg.	Agent	Solution, per Cent	Total, Cc.	Cc. per Kg.	Total, Gm.	Gm. per Kg.	Cc. per Min.
36	2.3	NaCl	10.0	23.0	10.0	2.3	1.0	1.0
50	2.4	$NaHCO_3$	9.0	48.0	20.0	4.3	1.8	1.0
13	2.5	Na citrate	20.0	9.2	3.7	1.85	0.74	Intermittently
29	2.3	Na citrate	20.0	16.3	7.1	3.3	1.43	0.2
49	2.2	NaI	21.7	22.0	10.0	4.8	2.2	1.0
49	2.2	$CaCl_2$	9.0	22.0	10.0	2.0	0.9	1.0
39	2.7	Menthenamine	40.0	32.0	12.0	13.5	5.0	Intermittently
25	3.5	Menthenamine	40.6	55.0	15.0	22.0	6.3	2.0
26	3.1	Dextrose	50.0	125.0	40.0	62.5	20.0	1.0
33	3.75	Acacia	6.0 25.0	98.0	26.0	10.0	2.7	1.0
48	3.8	Acacia	25.0	61.0	16.0	15.2	4.0	0.7
34	2.0	Peptone	10.0	25.0	12.5	2.5	1.25	0.5
27	2.6	Agar	0.1	13.0	5.0	0.13	0.05	0.1
31	2.7	Histamine	0.01	27.0	10.0	0.0027	0.001	0.25
40	3.0	Gelatin	5.0	30.0	10.0	1.5	0.5	0.3

(1 cc. equals 0.1 mg.) was infused slowly and continuously over a period of one hundred minutes (1 cc. in four minutes). The blood pressure of the animal was higher at the end than at the beginning of the infusion. The respirations were unaffected. The only variations were due to pinching the rubber tubing in order to accelerate the flow occasionally. Each of these pinches was accompanied by a marked fall in blood pressure, verifying the potency of the drug. In another experiment, 10 cc. of horse serum was infused slowly into guinea-pigs sensitized ten days previously. No evidences of anaphylaxis occurred. Later, 0.1 cc. was injected rapidly, and the animals died of typical shock. These two experiments emphasize the importance of velocity in producing changes in concentration sufficient to negate the reaction of labile but potent substances. Infused under the circumstances described that threshold value could not be reached for the rate of disappearance of the histamine must have at least equaled the intake.

Toxicity figures are also open to criticism when the nonspecific symptoms of speed shock have been attributed to inert agents employed rather than to the technical error of too rapid injection. Thus Hanzlik and Karsner speak of the toxicity of hexamethylenamine, agar, peptone, Fuller's earth, hypotonic and hypertonic saline, acacia, etc., whereas the symptoms produced are nonspecific and, unlike the histamine, not cumulative, unrelated to threshold value or concentration and are due wholly to the speed of injection.

NECESSITY OF STANDARDIZING VELOCITY

The velocity of injection should be standardized both in the laboratory and in the clinic. We do not belive that any single rate can cover all drugs. For obviously hypertonic solutions should be given slower than isotonic and large molecules slower than small molecules. Again, inert substances (saline, dextrose and acacia) may be given more rapidly than slightly active substances such as methenamine or arsphenamine. These in turn can be given more rapidly than potent substances such as histamine, epinephrine, etc. Toxic substances such as copper sulphate, etc. must be given intermittently as well as slowly if they are to be given at all. An ideal rate would be one that eliminated the possibility of speed shock and yet permitted the drug or agent to reach its threshold value and give its specific effect. We suggest that in pharmacologic assays, at least, a rate of 1 cc. per minute should be accepted as standard. In the clinic this rate would be impracticable for an infusion of 500 cc. would take eight or ten hours to complete. For clinical purposes, 2 or 3 cc. should be the upper limit for amounts of over 100 cc. and 1 cc. a minute for smaller amounts. These figures should not be regarded as the last word, but are to be regarded as a first attempt to standardize the velocity of intravenous injections.

POSSIBLE CLINICAL VALUE OF INTRAVENOUS DRIPS

With slow infusions (intravenous drips) such as we have described, it may be possible to give much larger quantities of useful substances (acacia, dextrose, methenamine, serums, etc.) without the hazard of the nonspecific speed shock reactions or even of true anaphylaxis. The huge amounts of fluid that can be handled in this way also demonstrate the extraordinary equilibratory mechanism in the body for handling fluid. The bulk reaction is easily recognizable and not dangerous. It may be abolished by intermittent infusion or a slow rate. The possibility of applying these suggestions to the treatment for shock and

hemorrhage and in serum therapy is especially suggestive. We suggest to clinicians who may be interested to follow these suggestions that the vein be exposed and a large sized cannula tied in with ligatures. The fluids may be run in from a buret or reservoir and need not necessarily be heated. An electric pad wrapped around the terminal rubber tubing may be an added protection. It is conceivable that such an intravenous drip will prevent "speed shock," anaphylactoid reactions, nitritoid and hemoclastic crisis, posttransfusion reactions, peptone shock and the sudden deaths,[25] described as following intravenous injections. It is not even too much to hope that the true anaphylaxis [26] may be avoided.

SUMMARY

1. A slow intravenous drip permits of the introduction of huge quantities of fluid and agents of all sorts.

2. Even toxic products may be introduced with impunity, especially if the injection is interrupted.

3. The practical value of these observations in the prevention of "speed shock," anaphylaxis, anaphylactoid and allied biologic reactions is discussed.

Throughout these studies we have had the constant aid of Prof. Charles C. Lieb.

25. Hanzlik and Karsner (footnote 1, first reference).

26. Lewis (footnote 1, sixth reference).

REACTIONS FOLLOWING TRANSFUSION OF BLOOD, WITH URINARY SUPPRESSION AND UREMIA*

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INTRODUCTION

For more than 250 years those who have attempted to restore health by the transference of blood from a normal to a diseased person have been keenly aware of certain attending dangers. As early as 1667, Jean Baptiste Denys described in vivid style [1] the outstanding features of the so-called hemolytic transfusion reaction, which until recently served as an inexplicable and insuperable barrier to the transfusion of blood. An understanding of the nature of the incompatibilities that are responsible for these frequently fatal reactions came only after the studies of Landsteiner [2] on hemagglutination in 1901; a simple method for determining compatibility grew out of the classifications of Jansky (1907) and Moss (1910). As a result of these discoveries, transfusion of blood became a popular therapeutic procedure at about the time of the World War; today, provided one has taken the necessary precautions in preliminary grouping and cross-agglutination tests, it is a procedure relatively free from danger. Nevertheless, transfusion reactions still occur, and although some of them are undoubtedly due to carelessness in the preliminary steps, it has been learned that certain reactions, most of them mild but others severe and fatal, cannot be clearly explained on the basis of the obvious incompatibilities discovered by Jansky and Moss.

In order to separate the unimportant from the serious transfusion reactions, recent authors have made an effort to formulate a classification of the various types. The classifications are for the most part symptomatologic, and are designed for the guidance of the operator of the transfusion; they deal primarily with the occurrences during and immediately following the injection of blood; they distinguish the trivial incidents from the danger signs. Three broad types of reaction are set forth: the "incompatible," the "citrate" and the "allergic." The

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1. Denys' patient, after a severe immediate reaction with paresthesia, sweating, lumbar pain, smothering sensations and vomiting, "fell asleep about 10 o'clock." The next morning he seemed improved and "made a great glass full of urine, of a color as black as if it had been mixed with the soot of chimneys" (Keynes, Geoffrey: Blood Transfusion, New York, Oxford University Press, 1922).

2. Landsteiner, K.: Ueber Agglutinationserscheinungen normalen menschlichen Blutes, Wien. klin. Wchnschr. **14**:1132, 1901.

names would imply that the classification is etiologic, but the etiology cannot be well established except for the first of the three. The type of reaction originally described so well by Denys is the "incompatible"; it is nearly always associated with agglutination or hemolysis of the donor's cells by the recipient's serum; in many cases, it will prove fatal unless the early manifestations are observed by the operator. The "citrate" reaction is generally characterized by a still unexplained, slightly delayed febrile response; it is a common enough reaction even when the blood is given without the citrate and it fortunately seems harmless. "Allergic" reactions may take the form of urticaria, asthma, localized edema, severe shock or some other phenomenon belonging to the allergic group. Certain other less common reactions do not fall readily into any orderly arrangement.

This classification of transfusion reactions is inadequate in one important respect: It does not tell the complete story of the reacting recipient. One is left to wonder what happens to the person who receives blood that is not suited to his circulation and who, nevertheless, does not die immediately. Does he always void "a great glass full" of sooty urine and then go on to a speedy recovery? Does he remain ill for some time and recover by slow stages? Does he linger on and die days or weeks later? A partial answer to these questions will be found in this paper, which presents a number of cases in which the reactions following the transfusion were greatly prolonged or delayed for several days.

The subject of delayed reactions following transfusion is not entirely new; a number of clinical and pathologic details have been outlined in case reports by various authors. Just where these prolonged or delayed reactions fall into the common classifications it is difficult to say. From the available data one is led to believe that most of them, perhaps all, are due to the use of demonstrably incompatible blood. Many of them originated with the classic reaction of Denys. Whether or not they all belong to the same etiologic group, they certainly have many points in common, and the outstanding feature is nearly always urinary suppression with uremia. When it is realized that a large proportion of the serious reactions that have been reported since 1924 are of this delayed type, the matter seems well worth review.

In the following pages, a detailed description will be found of three cases that were seen by the staff of Johns Hopkins Hospital and that are reported for the first time.[2a] For purposes of comparison

2a. Of these three cases I saw only case 1. The clinical observations on cases 2 and 3 were made by other members of the hospital staff to whom I am indebted for many of the data presented in the succeeding parts of this paper. Dr. Warfield T. Longcope was responsible for focusing our attention on the transfusion when case 1 first showed signs of uremia, and his very full notes on case 2 made it possible to trace accurately the various clinical events after a lapse of six years.

and study, fourteen other cases have been gathered from the literature and are presented in tabulated form. Space will not allow a full abstract of the cases of other authors, but those who care to refer to the original descriptions cannot fail to be struck by the similarity of the clinical course in almost all of them. Brief mention is made of several cases that undoubtedly belong to this group, but of which the available descriptions are too scanty to permit profitable tabulation. All the cases included for discussion have been reported in recent years since the introduction of modern methods of transfusion. No serious effort has been made to study systematically the literature prior to the recognition of blood groups. It is of interest to know that reactions with severe renal involvement occurred during the course of the earlier experimental work. Ponfik,[3] in 1875, gave a full description of reactions of this kind in dogs given transfusions of foreign blood. Lévy[4] (1904), in an investigation of the renal changes found in experimental hemoglobinuria, cited a number of earlier contributions to the study of this subject. Lindau[5] (1928) presented a large bibliography which covered many of the more recent studies.

REPORT OF CASES

Case 1.—A white woman, a housewife, aged 46, was admitted to the medical service of Johns Hopkins Hospital on April 1, 1929, complaining of weakness, loss of weight and insomnia. She had had pneumonia in childhood but no other serious illness. There was no suggestion of previous nephritis or disease of the urinary tract. She had been married at 23 years of age, and had five healthy children, the youngest being 7 years of age. Following the birth of the last child, there had been a definite change in menstruation, the flow becoming more profuse and lasting seven days. She began to "fail" about two years before admission, when her appetite became poor and she had insomnia. After that there had been increasing pallor, nervousness, palpitation and finally shortness of breath on exertion and edema of the ankles. The loss of weight had been 50 pounds (22.7 Kg.) in two years, her weight dropping from 150 pounds (68 Kg.) to 100 pounds (45.4 Kg.)

Physical Examination.—There was great emaciation, and profound pallor of the skin and mucous membranes. There was no jaundice or enlargement of the superficial lymph nodes. The patient had many carious teeth. The heart was a trifle enlarged to percussion; the apex impulse was readily visible; there was a loud systolic murmur of maximum intensity in the pulmonic area. The pulse was full, with a rate of 100 per minute. The blood pressure was 105 systolic, and 45 diastolic. The abdominal muscles were relaxed and atonic. The margin of the liver was palpable; the spleen was definitely enlarged, extending from 4 to 5 cm.

3. Ponfik: Experimentelle Beiträge zur Lehre von der Transfusion, Virchows Arch. f. path. Anat. **62**:273, 1875.

4. Lévy, L.: Untersuchungen über die Nierenveränderungen bei experimentelle Hämoglobinurie, Deutsches Arch. f. klin. Med. **81**:359, 1904.

5. Lindau, A.: Reaktionen nach Bluttransfusion. Eine ätiologische und pathologisch-anatomische Studie, Acta path. et microbiol. Scandinav. **5**:382, 1928.

below the costal margin, with the edge rounded, smooth and firm. Both kidneys were readily palpable. The vaginal outlet was relaxed; there was a profuse, yellowish, foul-smelling leukorrhea. The cervix was soft and patulous and the fundus of the uterus was slightly enlarged. Moderate pitting edema was found over both tibiae.

The urine, on admission, was acid, with a specific gravity of 1.012; analysis revealed albumin ++, many leukocytes and a few granular and hyaline casts but no red blood corpuscles. The blood test showed: hemoglobin, 20 per cent; red blood cells, 1,800,000; white blood cells 5,000 with a normal differential count. In the smears the red corpuscles appeared pale, and there was marked poikilocytosis. There was 0.6 per cent reticulocytes and the platelet count was 332,500. The bleeding and clotting times were normal. The fragility of the erythrocytes was within normal limits. The Wassermann reaction of the blood was negative. The van den Bergh reaction was indirect showing 0.2 mg. of bilirubin per hundred cubic centimeters. The nonprotein nitrogen content was 20 mg. per hundred cubic centimeters; the uric acid, 2.7 mg., and the blood sugar, 87 mg. The phthalein excretion was 65 per cent in two hours. Gastric analysis showed no free hydrochloric acid after stimulation with histamine. Roentgenologic studies of the chest and the entire gastro-intestinal tract revealed nothing of importance.

It was decided that the anemia was probably due to loss of blood from the uterus, and in order to prepare the patient for a uterine curettage and a possible laparotomy, blood transfusion seemed the procedure of choice. Previous to the transfusion the albuminuria had subsided to a bare trace and the casts had disappeared.

The patient and the selected donor were both reported by the laboratory to be members of group II (Moss). Direct matching of the blood showed no cross-agglutination after two hours. After the transfusion this work was all rechecked and it was found that after standing two hours the cells of the donor showed slight agglutination in the recipient's serum. Regrouping revealed the fact that whereas the donor was of group II, the recipient was of group IV (Moss). Fresh, citrated blood was used for the transfusion, which was begun early in the afternoon of April 5. The events that accompanied the injection of blood are of such interest that they will be related in detail.

Transfusion and Immediate Reaction.—The injection, which was controlled by a 20 cc. syringe, proceeded slowly. During the introduction of the first 20 cc. there was an abrupt fall in pulse rate from 90 to 70 per minute, and the patient complained of "creepy sensations" all over her body. She said that her head felt full and tight "as though it were going to burst." The subjective change seemed so definite that five minutes was allowed to pass before the injection was continued. A second 20 cc. was introduced cautiously. The pulse rate, which had risen to 90, again fell to 70 and the patient complained of a severe headache. Her face became suffused; there was fulness of the veins of the neck; respiration grew shallow and labored; she became nauseated and soon vomited. The blood pressure at this stage was 120 systolic and 60 diastolic, just where it had been the previous day. It was decided to discontinue the transfusion and the needle was removed from the vein. After an interval of twenty minutes, the patient announced that she was feeling fine. We were so confident of our blood matching that the transfusion was resumed. It took five minutes to inject the third 20 cc. and during this period, although the pulse fell from 90 to 60, there were no untoward symptoms, and the blood pressure remained at 120 systolic and 60

diastolic. After a pause of five minutes, the fourth 20 cc. was injected and again the pulse fell from 90 to 70. In five minutes the pulse had returned to 90. There were no symptoms as the fifth injection of 20 cc. was started. Scarcely 10 cc. had been injected when the patient suddenly complained of lumbar backache, fulness of the head, nausea and faintness. She became short of breath and cyanotic; the pulse rate rose rapidly and the beats could barely be detected at the wrist. The transfusion was discontinued at 4:30 p. m., after a total of 90 cc. had been injected.

At 4:45 p. m. there was a violent chill and the patient had an involuntary stool. The temperature was 101.8 F., the pulse rate 128 and the respiratory rate 26. At 5:15 p. m. the chill ended, but cyanosis was still marked and respiration was rapid and deep. There was considerable spontaneous bleeding from the venipuncture wounds in both arms, which could be controlled only by the application of pressure bandages. At 5:30 p. m., the temperature was 104.6 F., the pulse rate 142 and the respiration rate 38. At 6:00 p. m., she said that she felt warm and sleepy; she was perspiring freely and the temperature was 106 F. By 7:00 p. m., the temperature had fallen to 104.6 F., the pulse rate to 118 and the respiration rate to 28; cyanosis had disappeared and she was breathing freely. At this point moderate vaginal bleeding was first noted (menstruation was not due until seven days later). After a night's sleep, she felt fairly well. At 5:00 a. m., April 6, she voided 100 cc. of coffee-colored urine, containing much hemoglobin, albumin +++, a few red blood cells and no casts. At 6:00 a. m., the temperature was 100.8 F., the pulse rate 98 and the respiration rate 22. At 8:00 a. m., she again voided 100 cc. of dark brown urine. She complained of anorexia and nausea and vomited at noon. At 5:00 p. m., she passed 25 cc. of dark urine. In spite of the fact that the temperature had risen to 102 F., she felt better in the evening and ate a good supper.

Posttransfusion Course and Delayed Reaction.—The course can best be followed in figure 1.

On April 7, 8, and 9, the patient seemed to be recovering satisfactorily from what was thought to be a hemolytic "incompatible" transfusion reaction. The hemoglobinuria, jaundice, and vomiting, which had been striking features on the day after transfusion, subsided rapidly and finally disappeared. Transfusions of citrated group IV (Moss) blood on April 7 and 9 (550 and 500 cc., respectively) were followed by mild "citrate" reactions without additional symptoms. Urinary suppression, which was marked on April 7 and 8, attracted little attention at the time. On each of these two days there was only a single small voiding which unfortunately was not measured.

In the afternoon of April 9 (the fourth day after transfusion), though she seemed to be improving in every respect, the patient displayed a peculiar apprehension. She said that she had a "funny feeling" in her head and that there were films before her eyes. She announced that she was going to die, and despite reassurance persisted in this opinion. On April 10, apprehension and agitation became more marked; that night she carried on a lengthy, rambling conversation with a neighboring patient which she did not remember on the following morning. She was continually talking of death. On the night of April 11, she talked irrationally, and her husband told us that she seemed to him "entirely out of her head." On the morning of April 12, she decided that she did "not wish to die in the hospital" and insisted on being taken home. Aside from these queer and unexplained mental reactions, the patient appeared to be doing well. At 4 p. m. on April 12 (8 days after the transfusion), she suddenly had a generalized convulsion lasting 15 minutes and passed into a state of semicoma. In the evening she became completely comatose and had frequent generalized convulsions

At 7:00 p. m., large, bruiselike, purplish spots appeared on both arms and a small, fresh hemorrhage was seen in the fundus of the left eye. A few hours later, a fine petechial eruption was noted at the base of the neck. Studies of the blood at this point showed normal bleeding and clotting times, with normal retraction

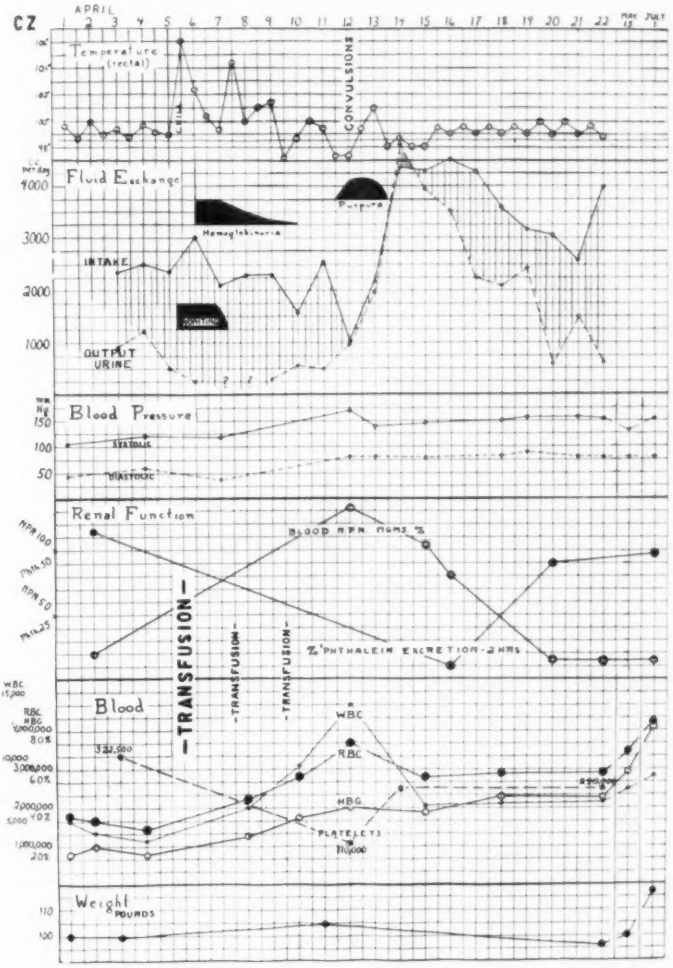

Fig. 1 (case 1).—Course of a patient belonging to group IV (Moss) who received 90 cc. of blood from a donor belonging to group II. There was an immediate reaction with chill, fever and vomiting, soon followed by hemoglobinuria and urinary suppression. Uremic manifestations, including convulsions and coma, appeared on the eighth day. Recovery was associated with diuresis.

of the clot. The platelet count, however, had fallen to 110,000. The van den Bergh reaction was negative. There had been a remarkable rise in blood nonprotein nitrogen to 132 mg. per hundred cubic centimeters.

Early in the morning on April 13, she regained consciousness. At 9:00 a. m., she was oriented but drowsy and listless. The urine showed a trace of albumin and a few red blood corpuscles. Together with the symptomatic improvement on that day, the urinary suppression gave way to diuresis, which on the next day amounted to 5,000 cc. of urine in twenty-four hours. As the diuresis progressed the patient cleared mentally and the blood nonprotein nitrogen content fell gradually to normal. The details of the clinical course are clearly indicated in figure 1.

Additional studies which do not appear in the chart are: On April 16, examination of blood showed: uric acid, 5.4 mg. per hundred cubic centimeters; creatinine, 2 mg.; carbon dioxide combining power of plasma, 49.4 per cent by volume and phosphorus, 7.5 mg. per hundred cubic centimeters. On April 23, the cerebrospinal fluid showed neither cytologic nor serologic abnormality.

By April 25, the patient had completely recovered from the effects of the delayed transfusion reaction.

Subsequent Course.—On May 9, she seemed in excellent condition for operation and was sent to the gynecologic service where a dilation and curettage operation was performed, and a cervical polyp removed. The gynecologic diagnosis was: hyperplasia of the endometrium, benign cervical polyp and chronic endocervicitis.

When discharged from the hospital on May 15, the patient's blood was well above its level on admission; the nonprotein nitrogen content had fallen below 30 mg. per hundred cubic centimeters. The phthalein excretion had risen to 50 per cent in two hours; the urine was entirely normal and the blood pressure was 134 systolic and 80 diastolic.

After discharge she returned to the hospital frequently for follow-up examinations. When seen on July 1, she seemed perfectly well, had gained 20 pounds (9 Kg.) in weight, and the blood picture, urine, phthalein excretion and nonprotein nitrogen of the blood were all entirely normal (fig. 1).

Summary.—A transfusion with 90 cc. of incompatible blood was followed by an immediate reaction with shock, chill, fever, vomiting, hemoglobinuria, jaundice and urinary suppression. The acute symptoms subsided but the urinary suppression continued. A secondary, delayed reaction, which reached its peak on the eighth day after transfusion, was characterized by agitation, psychosis, hypertension, reduced phthalein excretion, nitrogen retention, purpura, convulsions and coma. Recovery began on the ninth day and was associated with considerable diuresis. Three months later the patient was well.

CASE 2.—A white man, aged 52, had been sick for about three years: he was first admitted to the Johns Hopkins Hospital in July, 1922. The diagnosis was pernicious anemia. The blood examination showed: red blood cells, 1,200,000; hemoglobin, 32 per cent, and white blood cells, 5,200. The urine was normal. The phthalein excretion was 57 per cent in two hours. The blood was found to be group IV (Moss). The patient was given five transfusions of blood from group IV. He was discharged much improved, showing red blood cells 4,000,000, hemoglobin 60 per cent and white blood cells 8,000. He was readmitted to the hospital on Jan. 26, 1923, during a relapse. On January 28, he was prepared for transfusion. In the existing record there is no laboratory report of blood-grouping or cross-matching previous to this transfusion, though from the established practice in the hospital and the remarks in the record, one may presume that cross-matched group IV (Moss) blood was utilized. The important data following this transfusion are presented in figure 2.

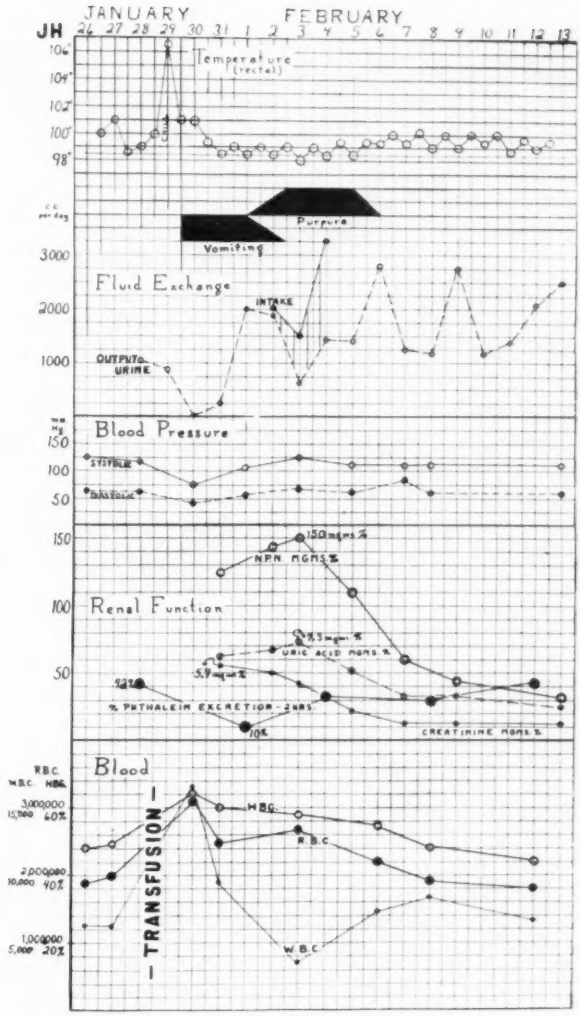

Fig. 2 (case 2).—Course of the reaction of a patient who was given 500 cc. of blood which was probably incompatible. Note the similarity between the chart of this patient and the chart in case 1.

As I did not see the patient, I quote the progress notes from the record:

January 28: The patient received 500 cc. of citrated blood; about thirty minutes later there was a slight chill. In one hour the temperature was 100.4 F., in two hours, 104 F. and in three hours 106.7 F. There was considerable nausea and some vomiting. Morphia quieted him and in four hours the temperature was 104 F., but the heart sounds were weak; at times they were slow and at other times rapid. The blood pressure could not be determined and the patient was practically pulseless at the wrist.

January 31: The patient was more deeply jaundiced. He voided 275 cc. of urine, the first since the transfusion (?). The urine contained red blood cells, casts, albumin and a great quantity of urobilin.

February 1: A fine hemorrhagic pruritic eruption appeared on the arms and legs.

February 2: The patient seemed better; his color was not so yellow. The rash was slightly elevated and did not fade on pressure. It was composed of pinpoint hemorrhagic spots.

February 3: The patient was weak and still nauseated, but severe vomiting had not been present since January 31. He had no appetite. The purpuric eruption was extensive and bright. It was almost confluent over the inner surface of the calves and the right forearm. The pectoral folds, the inner surface of the thighs, the buttocks and the inner aspect of the left elbow were thickly peppered with fine, bright petechiae. The abdomen and the chest were sparsely sprinkled with petechiae. The nose had been irritated and a thin blood-tinged fluid was occasionally blown out. There were no hemorrhages in the conjunctival or the buccal mucosa. The eyegrounds showed no hemorrhages.

February 5: The patient was much improved. The nausea had diminished. There was less jaundice and the rash was fading.

February 6: The purpuric eruption had disappeared.

The patient ultimately recovered from this reaction and returned home without another transfusion. On February 15, about two weeks after the transfusion, agglutination tests were made and it was noted that "the patient now shows group II (Moss) blood." It is of interest that there were two subsequent admissions to the hospital in 1923 and 1924. The blood was always found to belong to group II (Moss), but there was much difficulty in obtaining proper cross-matching with prospective donors. He was given five large transfusions with group II (Moss) blood, some followed by mild reactions and others without symptoms. He died during a violent immediate reaction on April 10, 1924, following the injection of 250 cc. of group II cross-matched blood.

Summary.—A transfusion with 500 cc. of what was probably incompatible blood was followed by an immediate reaction with chill, fever, collapse, vomiting, jaundice, urinary suppression and urobilinuria. Following this, there was a delayed reaction which reached its peak on about the eighth day after the transfusion and which was characterized by purpura, nitrogen retention, reduced phthalein excretion and slight rise in blood pressure. Recovery was coincident with a rise in the phthalein excretion and a fall in the nonprotein nitrogen content of the blood.

CASE 3.—A white man, aged 39, was first admitted to the Johns Hopkins Hospital in October, 1920, during the fourth relapse of a characteristic pernicious anemia. In the hospital the disease underwent spontaneous remission. He was discharged after the blood had improved from a red blood cell count of 1,648,000 with 42 per cent hemoglobin, to a red blood cell count of 3,768,000 with hemoglobin, 75 per cent. The urine was normal. The patient was readmitted on May

20, 1922, during the seventh relapse. The blood showed: red blood cells, 1,336,000; hemoglobin, 30 per cent, and white blood cells, 4,000. The blood was found to be group IV (Moss).

On May 29, utilizing blood which had been tested for cross-agglutination, a transfusion was attempted but was stopped immediately because "the patient became cyanotic, his face began to swell, his breath came with difficulty and he finally collapsed." On June 10 he was given a transfusion of 750 cc. of citrated blood without an immediate or subsequent reaction. On June 30, a third transfusion was undertaken with blood that had previously been tested for cross-agglutination. The more important features of the course following transfusion are recorded in figure 3. As I did not see this patient, I quote the following remarks from the progress notes in the record.

June 30: The patient was given a transfusion. After 50 cc. had been injected, the patient began to complain of a smothering sensation. Atropine, 0.01 grain (0.00065 Gm.), and epinephrine, 15 minims (0.92 cc.), relieved this and the injection proceeded. After 350 cc. had been injected the patient vomited and had a chill and the injection was stopped. The temperature rose to 104.5 F. and the patient could retain nothing by mouth for eight hours.

July 1: The urine was clear and straw colored, it contained no albumin. The guaiac reaction was negative.

July 2: The reaction from the transfusion had subsided, but the patient still complained of nausea.

July 4: For forty-eight hours the patient had been unable to retain anything by mouth.

July 6: The urine was acid, with a specific gravity of 1.020, albumin + and the guaiac reaction negative.

July 7: The patient had vomited for three days. Since the day before, his respirations had been deep and slow; hyperpnea was pronounced and the patient was drowsy.

July 8: The urine was acid, containing albumin ++++, and hyaline and granular casts. The guaiac reaction was negative. The blood showed: nonprotein nitrogen, 186.3 mg. per hundred cubic centimeters, and carbon dioxide combining power, 18.7 per cent by volume.

July 10: The blood showed: nonprotein nitrogen, 186 mg. per hundred cubic centimeters; sugar, 123 mg.; creatinine, 10.1 mg.; chloride, 486 mg., and carbon dioxide combining power, 22.5 per cent by volume. For twenty-four hours there had been marked oliguria, a state of semicoma and convulsions. The patient could not be roused. There were tracheal râles. He had labored breathing. The face had a curious suffused look. No jaundice was apparent. He gave some evidence of discomfort on pressure in the right upper abdominal quadrant. Shortly after this note was made, the patient died.

Autopsy.—In addition to the changes in the liver and kidneys, which will be described in detail, the following points are of interest: There was slight edema of the ankles, general pallor of the organs, well preserved subcutaneous fat which had a characteristic bright, lemon-yellow tint, bilateral hydrothorax (300 cc. on each side) and a few small areas of fresh lobular pneumonia. The spleen was enlarged (520 Gm.). In microscopic preparations there was no striking abnormality of the spleen; the malpighian bodies and venous sinuses stood out sharply; many erythrocytes were in the sinuses and scattered through the reticulum; there were a few scattered myelocytes, mostly eosinophilic. The bone-marrow was hyperplastic, containing many normoblasts and megaloblasts and a moderate number of megalokaryocytes.

The liver was large (2,600 Gm.); its surface was smooth and grayish red with indistinct lobulation. For microscopic study only hematoxylin and eosin preparations were used; the tissue was not available for other stains. The lobules were arranged normally and the parenchymal cells were cloudy; many small vacuoles were apparently due to deposits of fat. Nearly all of the cells, but particularly those of the periportal areas, were sprinkled with fine, yellowish-brown pigment

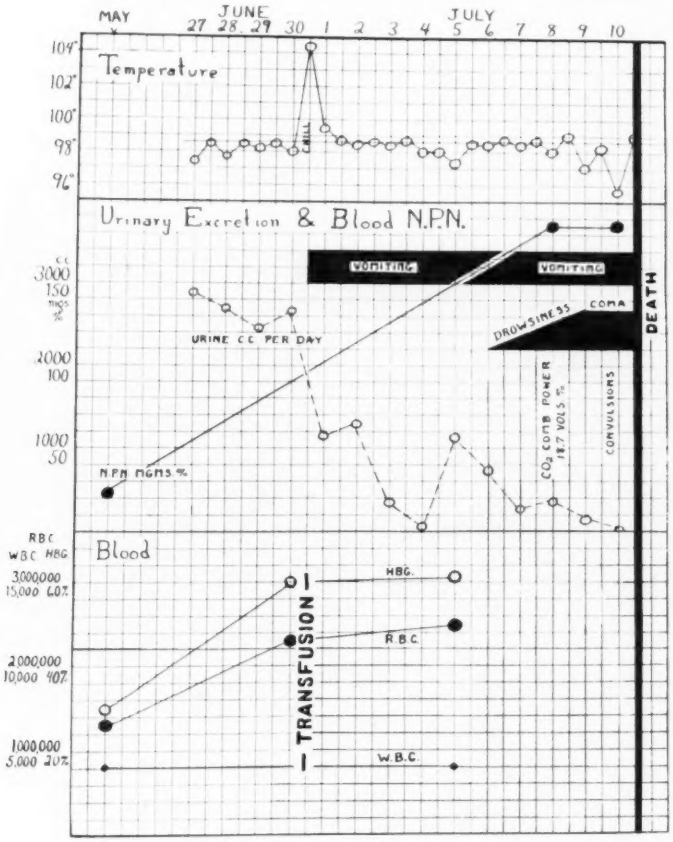

Fig. 3 (case 3).—Course of a patient who was given a transfusion of 350 cc. of blood. An immediate reaction was followed by persistent vomiting and oliguria. Uremic manifestations developed gradually and the patient died on the eleventh day.

granules. There was distinct central atrophy, and in addition a number of central necroses, in some of which the nuclei were no longer visible and the normal cellular structure had been replaced by smooth hyaline and fibrous tissue, in which there was a scattering of lymphocytes and a few large, pigment-laden mononuclear cells with shrunken nuclei.

The kidneys were large, the right one weighing 289 Gm. and the left one, 300 Gm. The capsule stripped easily leaving a smooth, grayish-red, glistening surface. The cortex was 7 mm. in thickness, dull, yellowish gray and rather translucent; the striae were fairly distinct. The glomeruli were readily visible as pale yellow, translucent elevated dots. The pyramids were of much deeper red color. Several small, dark red hemorrhages were present in the mucosa of the right renal pelvis. The ureters were patent. Microscopic examination showed the capsular surface to be regular. The tubules were widely separated by loosely arranged, edematous tissue, in which only a few delicate strands took up the pink of the van Gieson stain. There were a few inconspicuous, old fibrous scars containing clumps of lymphocytes. There was a remarkable cellular

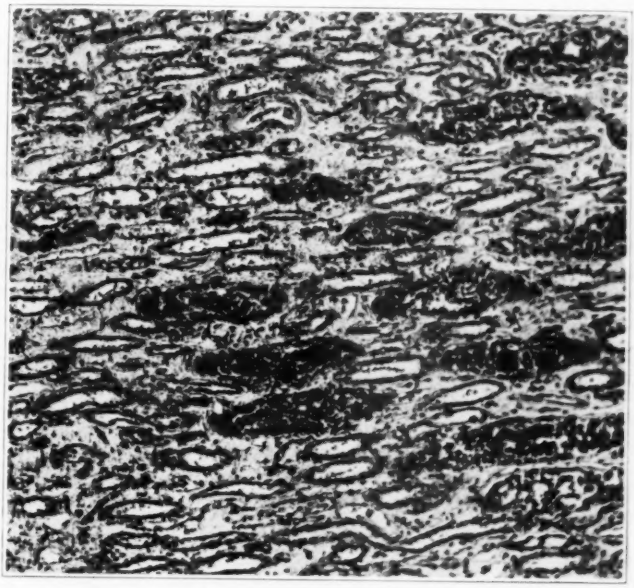

Fig. 4 (case 3).—Photomicrograph of the kidney, showing a group of collecting tubules, many of them containing blood pigment, cells and débris; × 90.

infiltration throughout the edematous interstitial tissue, most of the cells were lymphocytes, but there were a number of small groups, some of them periarterial, in which there was a striking number of large, mononuclear wandering cells and polymorphonuclear leukocytes. The arteries and veins were not remarkable. The glomeruli appeared large, with a relatively wide intracapsular space. A few glomerular capsules showed slight fibrous thickening, but the capillary tufts were everywhere normal and there was no evidence of acute or progressive glomerular disease. After examining many sections it was possible to demonstrate two or three obliterated and fibrosed glomeruli. The tubules of the cortex had large lumina and flattened epithelial cells, in a few of which the cytoplasm was sprinkled with small grains and droplets of a brownish pigmented material. As one passed down the tubules toward the pelvis one found that the epithelial changes became more marked and that the cells grew larger and cloudier; they

were less firmly attached and contained more and larger droplets of brown pigment. In many of the collecting tubules the epithelial cells were packed with pigment droplets; they were frequently necrotic and in two or three places showed evidences of calcification. In some of the places where the necrotic epithelium had become detached, the tube was lined with a new layer of flat and apparently regenerating cells. The lumina of the cortical tubules contained nothing except occasionally a finely granular, pale, eosin-staining material and a few leukocytes. Following the tubules downward, one found their lumina filled with increasing amounts of débris, disintegrated leukocytes, desquamated epithelial cells and large phagocytic cells filled with yellowish-brown pigment. In addition to these there were, in increasing numbers, large and small globules of a conspicuous and peculiar material which requires more detailed consideration. In the

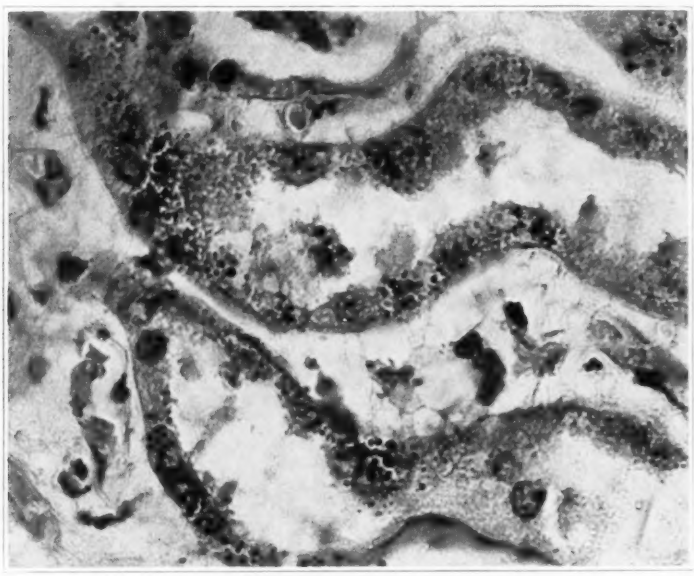

Fig. 5 (case 3).—Photomicrograph of the kidney, showing two tubules, the epithelial cells of which contain the brownish, pigmented droplets described in the text. The section was stained lightly in order to make the droplets stand out as sharply as possible; × 580.

proximal levels of the tubules these peculiar droplets had almost the same staining characteristics as the erythrocytes of the adjacent capillaries, though they stained more deeply with eosin and less brilliantly with fuchsin. That they were not erythrocytes became apparent from a study of their contour and from their great variations in size. Passing further down the tubules one found that these droplets became less and less eosinophilic, and less and less fuchsinophilic. In the large collecting tubules they had in unstained preparations a rusty brown color. When stained with a fuchsin-methyl green technic (Altmann's aniline fuchsin and methyl green) they had a muddy, greenish-brown hue in which there was occasionally the faintest tinge of pink. The pigmented droplets within the epithelial cells, to which attention has been called, had similar staining

characteristics. Various iron stains showed a few scattered granules in the epithelial cells which gave the characteristic iron color reactions (hemosiderin granules of pernicious anemia similar to those found in the liver); the peculiar pigmented droplets, on the other hand, both in the epithelial cells and within the lumina of the tubules, failed to take on the faintest trace of prussian blue.

Summary.—A patient with pernicious anemia was given a transfusion of 350 cc. of blood that was thought to be compatible. There was an immediate reaction with chill, fever, vomiting and suppression of urine. The acute symptoms subsided, but vomiting and oliguria continued. On the seventh day after transfusion, uremic manifestations were evident. On the eleventh day, nitrogen retention, acidosis and marked albuminuria were observed, and the patient died in a state of coma. At autopsy, the liver was large, contained considerable fat and fresh and healed central necroses. The kidneys were swollen, edematous and infiltrated with leukocytes. The renal epithelial cells showed a peculiar type of degenerative change in which the intracellular deposition of pigmented droplets was a conspicuous feature. Many of the epithelial cells were necrotic and there was a suggestion of epithelial regeneration. The tubules, especially the collecting tubules, contained large amounts of a similar pigmented material and in addition desquamated epithelial cells, leukocytes and granular débris.

Case 4 (Goormaghtigh[6]).—A man, aged 23, was given a transfusion four hours after being shot through the left axillary vein. The immediate response was excellent, but oliguria followed. On the third day, after an apparently normal course, agitation and vomiting set in. Death occurred on the sixth day with anuria and a manifest hypertension.

At autopsy, the liver showed degenerative changes in the central portion of the lobules. The kidneys were large and microscopic changes were confined to the tubules; the proximal convoluted tubules were dilated with a flattening of the epithelium; there was desquamation of the epithelium of the distal convoluted tubules; the collecting tubules were packed with débris.

Case 5 (Bancroft[7]).—A woman, aged 49, had an incomplete abortion with hemorrhage and secondary anemia. During transfusion she complained of pain in the lumbar region. Immediately after the transfusion, a chill and fever were followed by urinary suppresion. The oliguria continued and vomiting was persistent. The blood urea rose and the patient became edematous and irrational. On the eighth day there were "spastic contractions" of both hands resembling tetany. On the ninth day, the condition seemed desperate, and decapsulation of both kidneys was performed. Following the operation there was marked diuresis with gradual recovery. At operation the kidneys appeared "almost necrotic;" they were large, grayish and friable.

Case 6 (Oliensis[8]).—A woman, aged 23, had chronic sinusitis, epistaxis, and secondary anemia. Transfusion was followed by a severe immediate reaction, with shock, a chill, fever and vomiting; soon jaundice developed with urinary suppression. Following this there was continued oliguria and vomiting, nitrogen retention, anasarca, stupor, dimness of vision and delirium. Improvement was associated with diuresis that began on about the twelfth day. Recovery was gradual.

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6. Goormaghtigh, N.: Note sur un cas de bloquage du rein consécutif à la transfusion du sang, Arch. méd. belges **72**:611 (Dec.) 1918.

7. Bancroft, F. W.: Anuria following Transfusion: Effect of Decapsulation of Both Kidneys, Ann. Surg. **81**:733 (April) 1925.

8. Oliensis, A. E.: Acute Nephritis following Transfusion, M. J. & Rec. **128**:178 (Aug. 15) 1928.

Case 7 (Shera [9]).—A woman, aged 36, had a ruptured ectopic pregnancy. Following transfusion there was a mild immediate reaction with a slight fever. On the second day, hemoglobinuria and jaundice developed with urinary suppression. The oliguria continued, but for several days the general condition seemed good. Nitrogen retention was noted on the fourth day, and on the seventh day, signs of uremia appeared. A period of drowsiness and irritability was followed by sudden death on the ninth day.

At autopsy, the liver was found to be of the "nutmeg" type with "parenchymatous degeneration." The spleen was engorged. The kidneys were large and pale; the tubules were filled with red blood cells and débris and the tubular epithelium was flattened.

Case 8 (Lemke [10]).—A woman, aged 32, had a ruptured ectopic pregnancy. There was general improvement immediately after the transfusion but soon fever set in. From the day of the transfusion there was persistent vomiting, urinary suppression and epistaxis. The patient grew progressively worse, exhibited signs of uremia and died six days after the transfusion.

At autopsy, punctiform hemorrhages were found in the pleura and mucous membrane of the bladder. The liver showed numerous necroses located for the most part in the central portion of the lobules. The kidneys were pale; occasional glomeruli seemed swollen; the tubules were filled with cellular débris and finely granular or amorphous material giving the color reactions of hemoglobin; many collecting tubules were plugged with this material. The capillaries of the medulla were distended with blood; accumulations of small round cells were observed here and there between the tubules.

Case 9 (Santy [11]).—A woman, aged 30, had a ruptured ectopic pregnancy. The immediate results of a transfusion seemed favorable, but on the second day, urinary suppression and hemoglobinuria were noted. The oliguria persisted and on the eighth day, following the development of pulmonary edema, the patient died. There was anuria during the forty-eight hours before her death.

Case 10 (Boidin, Berthaux and Beyrand [12]).—A young woman had prolonged typhoid fever with progressive anemia. There was a violent immediate reaction following transfusion, with a chill, collapse, fever and vomiting, followed by urinary suppression and "red urine." The oliguria continued and vomiting increased on the fifth day. On the sixth day, following generalized convulsions, the patient became comatose; the coma lasted for four days. As consciousness was regained there was diuresis. The patient gradually returned to normal.

Case 11 (Baker and Dodds [13]).—A woman, aged 38, had a gastric ulcer. She was given a transfusion during the operative anesthesia. An immediate

9. Shera, G.: Fatal Suppression of Urine Caused by Latent Haemagglutinins, Brit. M. J. **1**:754 (May 5) 1928.

10. Lemke, R.: Pathologisch-anatomische Befunde bei Todesfällen nach Bluttransfusionen, Virchows Arch. f. path. Anat. **257**:415, 1925.

11. Santy, M. P.: Néphrite aiguë mortelle consécutive à une transfusion, Lyon chir. **23**:608, 1926.

12. Boidin, Berthaux and Beyrand: Petite transfusion de 40 centimètres cubes de sang citraté dans un cas de septicémie post-typhoïdique. Choc dramatique et accidents tardifs extrêmement graves, Bull. et mém. Soc. méd. d. hôp. de Paris **43**:869, 1919.

13. Baker, S. L., and Dodds, E. C.: Obstruction of the Renal Tubules during the Excretion of Haemoglobin, Brit. J. Exper. Path. **6**:247 (Oct.) 1925.

reaction was not noted, but the temperature rose after the operation. Following the development of hemoglobinuria, jaundice and urinary suppression, the patient's condition grew rapidly worse; coma set in and she died on the fourth day with marked nitrogen retention.

At autopsy the kidneys were pale; there was marked dilatation of Bowman's capsules and convoluted tubules with flattening of the epithelium of the latter. Small masses and granules of eosin-staining material were arranged loosely in the convoluted tubules but were tightly packed in the collecting tubules.

Case 12 (Baker and Dodds[13]).—A woman, aged 54, had jaundice and cholelithiasis. There was an immediate transfusion reaction with collapse and fever followed by hemoglobinuria, urinary suppression, increasing nitrogen retention, coma and death on the eighteenth day.

At autopsy, nodular cirrhosis of the liver was noted. A large stone was found in the common bile duct. The kidneys were dark brown; the glomeruli and the convoluted tubules were normal; the collecting tubules were filled with polymorphonuclear and mononuclear cells and much eosin-staining, granular debris.

Case 13 (Curtis[14]).—A young woman had myoma uteri with hemorrhage and secondary anemia. There was an immediate transfusion reaction with pain in the back and chill, followed by hematuria, urinary suppression and nitrogen retention. When last observed, two weeks after the transfusion, the patient was gradually recovering.

Case 14 (Copher[15]).—The age and sex of this patient were not stated. Secondary hemorrhage developed following a nasal operation. There was no immediate transfusion reaction, but shortly afterward persistent vomiting began and there was suppression of the urine. On the second day, hemoglobinuria developed, followed by jaundice and enlargement of the liver. Hemorrhagic retinitis developed and the patient died eleven days after the transfusion.

Case 15 (Witts[16]).—A woman, aged 29, had secondary anemia following pregnancy. During the transfusion she complained only of a headache. A few hours later there was vomiting and elevation in temperature. There was complete suppression of the urine until the sixth day, when the blood urea was 333 mg. per hundred cubic centimeters. Throughout this period "her color and appearance were good and her mentality clear." On the ninth day, hypertension and tetany developed. On the tenth day, the output of urine increased somewhat and the "condition of the patient seemed fair." At this time the blood urea was 354 mg. per hundred cubic centimeters and the plasma bicarbonate was 33.6 per cent by volume. Death came suddenly on the eleventh day.

At autopsy, anasarca with bilateral hydrothorax and ascites was discovered. The kidneys were swollen and pale and showed a few petechiae. The glomeruli were large and anemic. The convoluted tubules contained albuminous material. The junctional tubules contained deeply eosinophilic granules or small spheres. "Numerous collecting and junctional tubules" and "most of the discharging tubules" were filled with granules, lumps and masses of an "isotropic substance of the color of brown sugar"; in addition there were leukocytes and

14. Curtis, A. H.: Anuria following Blood Transfusion, Surg. Gynec. Obst. **30**:627, 1920.

15. Copher, G. H.: Blood Transfusion: A Study of Two Hundred and Forty-five Cases, Arch. Surg. **7**:125 (July) 1923.

16. Witts, L. J.: Note on Blood Transfusion with an Account of a Fatal Reaction, Lancet **1**:1297 (June 22) 1929.

desquamated epithelial cells. The cytoplasm of the desquamated cells was "finely granular and of the same color as the granules and lumps." The interstitial tissue was edematous and infiltrated with round cells. The change in the kidneys was spoken of as "hemoglobin infarction." The liver was not described.

Case 16 (Lindau [5]).—A man, aged 35, had a history of duodenal ulcer. He was given a transfusion because of a gastric hemorrhage following resection of the stomach. It was thought from the agglutination tests before the transfusion that the donor and the recipient both belonged to group IV (Moss). Subsequent to the transfusion, careful studies of the blood were carried out by Forssman and Fogelgren.[17] It was found that the recipient belonged to group IV (Moss) and the donor to group II (Moss). After 75 cc. of blood had been injected, the patient became pale and pulseless and lost consciousness. Because of this reaction the transfusion was stopped temporarily, but was soon resumed and a total of 450 cc. of blood injected. One hour later, there was a chill followed by fever and hemoglobinuria. During the next three days only from 20 to 50 cc. of urine was passed. The blood nonprotein nitrogen increased gradually and on the day of the patient's death it reached 234 mg. per hundred cubic centimeters. Death occurred during uremia on the sixth day after the transfusion.

At autopsy, there was no icterus, cutaneous hemorrhage or edema. The liver was of normal size; there was no gross abnormality; microscopically, a number of central and irregularly arranged necroses were found. The kidneys were slightly enlarged. There was the "nephrotic type" of degenerative changes in the epithelial cells of the renal tubules. There were masses of hemoglobin in the lumina of the collecting tubules; these were rose colored in the proximal levels and yellowish brown in the distal levels. The interstitial cellular infiltration of the kidneys was of such a character as to suggest foci of blood formation. A large ulcerated area was seen in the sigmoid portion of the colon. There were hemorrhages in the mucosa of the urinary bladder. Sero-sanguineous fluid was observed in the pleural and the peritoneal cavities.

Case 17 (Lindau [5]).—A woman, aged 28, had cholecystitis. There was hematemesis following cholecystectomy. The patient was somewhat restless during the early part of the transfusion but she soon became quiet. One hour after the transfusion, a chill was followed by fever and hemoglobinuria. From this point on, there was oliguria. On the sixth day, the blood nonprotein nitrogen reached 150 mg. per hundred cubic centimeters. The patient became stuporous, vomited a great deal and finally died in uremia on the tenth day.

At autopsy, there was a bilateral bronchopneumonia. The kidneys were somewhat swollen, and in microscopic studies they showed essentially the same changes described in case 16. The degeneration of the epithelial cells of the renal tubules was more advanced; there was epithelial desquamation and regeneration. The liver was not studied.[18]

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17. Forssman, J., and Fogelgren, G.: Ein Todesfall nach Bluttransfusion von Person zu Person mit "gleicher" Blutgruppe, Klin. Wchnschr. **6**:1663 (Aug. 27) 1927.

18. Lindau's case 3 (footnote 5) has not been included in this series. The patient was an old man very ill with hypernephroma, who died thirty-six hours after the transfusion. The clinical data are incomplete, but the autopsy observations are of great interest. The tubular epithelial cells of the kidneys showed early degenerative changes. Hemoglobin was found in the lumina of the loops of Henle, but practically none was present in the collecting tubules. The liver showed fresh foci of necrosis.

Additional Cases.—In addition to the foregoing cases, which have been summarized in table 1, brief mention should be made of several other reported cases in which the posttransfusion course was of the same character. Hirsch,[19] in a discussion of blood transfusion, mentioned a young woman who was given blood without previous grouping or cross-agglutination tests. Soon after the transfusion there was a chill, then jaundice and oliguria, and finally uremia, with death on the ninth day. Pribram[20] observed the same type of reaction, with oliguria and an extreme grade of nitrogen retention. Death occurred three or four days after the transfusion; at autopsy, masses of hemoglobin were found in the tubuli recti of the kidneys, completely occluding some of them. Enderlein[21] observed a person in whom transfusion was followed by anuria which continued until the patient's death three days later.

In a series of 4,000 transfusions Brines[22] had three cases in which this same peculiar reaction occurred. "The reactions were typical, consisting of a chill, an elevation in temperature, lumbar and abdominal pain, some dyspnoea and either oliguria or anuria. The blood urea became elevated, symptoms of uraemia were apparent, coma followed, and death intervened in from four to eight days." Brines said that "in all of these patients a previously well established diagnosis of chronic nephritis had been made." He mentioned no autopsy observations, and one is led to wonder just how much the chronic nephritis had to do with this "typical" reaction.

Lemke,[10] in addition to the case cited (case 8), reported one in which the patient showed a delayed reaction of a slightly different type. A transfusion with 1,000 cc. of blood that may have been incompatible was followed by a chill and fever. The temperature did not fall to normal; the patient became restless, then stuporous, and died on the tenth day. Throughout this time the urine was normal, and contained no trace of hemoglobin (the quantity of urinary excretion was not specifically mentioned). At autopsy, there were numerous hemorrhages throughout the mucous and serous surfaces. The liver showed necroses similar to those described in Lemke's first case (case 8). Aside from arteriosclerosis, the kidneys showed nothing of significance.

Butka[23] and Herrmann[24] reported cases in which delayed transfusion reactions were characterized by purpura with extensive hemorrhagic eruptions and bleeding from the mucous surfaces. One patient died six days, and the other three weeks, after the injection of the blood. In neither of these cases was urinary suppression specifically mentioned.

Grossmann[25] recorded the case of a woman, 24 years of age, who had a large intra-abdominal hemorrhage as the result of a ruptured fallopian tube. She was given a transfusion of 500 cc. of the bloody fluid obtained from the abdominal cavity. Shortly after the transfusion, hemoglobinuria was noted. This was followed by persistent oliguria and the patient died in uremic coma six days later.

19. Hirsch, M.: Wien. med. Wchnschr. **74**:1722, 1924.

20. Pribram, E.: Arch. f. klin. Chir. **133**:77, 1924.

21. Enderlein, quoted by Lemke (footnote 10).

22. Brines, O. A.: Fatal Post-Transfusion Reactions, J. A. M. A. **94**:1114 (April 12) 1930.

23. Butka, H. E.: Transfusion with Universal Donor. A Fatality, California & West. Med. **24**:74 (Jan.) 1926.

24. Herrmann, H.: Hämorrhagische Diathese nach Bluttransfusion, Med. Klin. **19**:722 (May 27) 1923.

25. Grossmann, H.: Eigenbluttransfusion mit tödlichem Ausgang, Zentralbl. f. Gynäk. **48**:2065 (Sept. 20) 1924.

Summary of Clinical Data

Case	Age	Sex	Diagnosis	Transfusion Data: Blood Group (Moss) Recipient	Blood Group (Moss) Donor	Cross-agglutination	Method	Amount, Cc.	Immediate Reaction: Chill	Fever	Urinary Suppression	Hemoglobinuria	Interval Phenomena: Oliguria	Jaundice	Vomiting	Delayed Phenomena: Purpura	Nitrogen Retention	Central Nervous System Symptoms	Additional	Climax Reached	Result	Comment
1	46	F	Menorrhagia, secondary anemia	IV	II	+	Citrate	90	+	+	+	+	+	+	+	+	−	Delirium, convulsions, coma	Fall in phthalein excretion, hypertension	8th day	Recovery	
2	52	M	Pernicious anemia	? II	IV	?	Citrate	500	+	+	+	0	+	+	+	+	+	0	Fall in phthalein excretion, edema	8th day	Recovery	Sixth transfusion
3	39	M	Pernicious anemia	IV	? IV	0	Citrate	350	+	+	+	0	+	0	+	0	+	Convulsions, coma	Acidosis	11th day	Death, autopsy	Third transfusion, second transfusion reaction
4	23	M	Hemorrhage, gunshot wound	?	?	?	Whole blood	520	0	+	+	0	+	? 0	+	? 0	? +	Agitation, syncope	Hypertension	6th day	Death, autopsy	
5	49	F	Uterine hemorrhage; secondary anemia	?	?	0	Whole blood	400	+	+	+	0	+	0	+	? 0	+	Delirium, "tetany"	Edema	9th day	Recovery	Improvement followed decapsulation of kidneys
6	23	F	Epistaxis; secondary anemia	? (same group)	?	0	Whole blood	540	+	+	+	? 0	+	+	+	? 0	+	Vertigo, psychosis	Marked anasarca	12th day	Recovery	
7	36	F	Ruptured ectopic pregnancy	IV	IV	+	?	500	0	+	+	+	+	+	? 0	? 0	+	Drowsiness, irritability	.....	9th day	Death, autopsy	Transfusion during general anesthesia
8	32	F	Ruptured ectopic pregnancy	II	II	?	Whole blood	1,000	0	+	+	+	+	? 0	+	? +	? +	?	Epistaxes	6th day	Death, autopsy	
9	30	F	Ruptured ectopic pregnancy	?	?	?	Whole blood	450	0	+	+	+	+	? 0	? 0	? 0	? +	?	Pulmonary edema	8th day	Death	
10	?	F	Typhoid fever; anemia	?	?	0	?	40	+	+	+	? +	+	? 0	+	? 0	? +	Convulsions, coma	.....	12th day	Recovery	
11	38	F	Gastric ulcer	?	?	+	?	750	0	+	+	+	+	+	? 0	? 0	+	?	.....	4th day	Death, autopsy	Transfusion during general anesthesia
12	54	F	Cholelithiasis	IV	IV	+	?	600	? 0	+	+	+	+	? 0	? 0	? 0	+	Drowsiness, coma	.....	18th day	Death, autopsy	
13	?	F	Uterine hemorrhage	?	?	0	Citrate	?	+	+	+	+	+	? 0	? 0	? 0	+	?	.....	? day	Recovery	
14	?	?	Nasal hemorrhage	IV	IV	+	Whole blood	620	0	0	+	+	+	+	+	+	?	?	Hemorrhagic retinitis	11th day	Death	
15	29	F	Secondary anemia	II	II	0	Citrate	?	0	+	+	0	+	0	+	? 0	+	"Tetany"	Anasarca, hypertension, acidosis	11th day	Death, autopsy	
16	35	M	Duodenal ulcer	IV	II	+	Citrate	450	+	+	+	+	+	? 0	? 0	? 0	+	?	.....	6th day	Death, autopsy	
17	28	F	Cholecystectomy, hemorrhage	?	?	0 ?	Citrate	400	+	+	+	+	+	? 0	+	? 0	+	Stupor	.....	10th day	Death, autopsy	

SUMMARY OF CLINICAL DATA

The Patient.—The series is made up of seventeen patients, most of them relatively young adults. Anemia of some kind was present in all of them, but the cause of the anemia, its severity and the general condition of the patient at the time of transfusion seem to have had little influence on the occurrence of a reaction or its ultimate outcome. Reactions occurred so frequently in young persons who had been well until the onset of a sudden and severe hemorrhage that it would seem reasonable to exclude chronic illnesses, such as nephritis, heart disease, etc., from an important rôle in the causation of the response.

The Donor.—In not a single case is there complete and satisfying evidence to prove that the blood of the donor was compatible with that of the recipient. Definite incompatibility was established in six cases. In two others (cases 4 and 9) there was probable incompatibility since transfusion was performed as an emergency measure without previous tests. The patient in case 2 seems to have presented an example of a queer change in blood group and was probably given incompatible blood. In case 8, cross-agglutination was not tested. In cases 3, 5, 10, 13 and 17, the statement is made that there was no cross-agglutination, but in none of these was the blood group of the donor determined; in only one was the recipient's group known. In case 6, the recipient and donor were of the same blood group (group not stated) and there was no cross-agglutination. In case 15, the recipient and donor were both of group II and there was no cross-agglutination. In none of the seven cases in which cross-agglutination was found satisfactory was there a retest of the agglutination reactions after transfusion, and the latter step, according to our experience in case 1 and Lindau's experience in case 16, would seem to be of considerable importance.

The Transfusion.—The methods used in preparing and injecting the blood seem to have been of little importance; citrate was used in about half of the cases. On the other hand, the amount of blood injected was a significant factor in determining the final outcome. A definite statement of the amount transfused was made in fifteen of the seventeen cases; ten of these patients died and five recovered. In the five who recovered, the average amount injected was 314 cc., whereas the ten who died received an average amount of 564 cc. No patient receiving less than 350 cc. died, and no one receiving more than 540 cc. recovered. The patient who survived after a transfusion of 540 cc. ran the most severe course of the recovered patients and until the twelfth day seemed on the verge of death.

Immediate Reaction.—A severe immediate transfusion reaction occurred in all but seven of the cases. Two of these seven were under anesthesia during the injection of the blood, and in them it is difficult

to attach much importance to the absence of this reaction. In at least six of the ten cases in which immediate reactions occurred, symptoms were first noted during the injection of blood, and in three of these the symptoms were of such severity that the injection was cut short. Detailed description of a fairly typical immediate reaction is presented in the history in case 1. The manifestations vary somewhat from case to case, but as a rule the characteristic features are a sense of great discomfort, signs of collapse, vomiting, chill and a sharp rise in temperature. The more acute symptoms rarely last more than a few hours, and as they subside hemoglobinuria is generally noted; it was observed in ten of the fifteen cases in which it was specifically looked for and it is possible that it was present in an eleventh instance in which the urine was described as "red." The first urine voided after the transfusion practically always contained albumin. Dating from the immediate reaction, there was suppression of urine in every one of the seventeen cases.

The Interval.—In all instances, with the subsidence of the immediate reaction the patients seemed to improve. This interval of improvement lasted from a day or two to about a week, during which the patients were brighter and appeared to have derived distinct benefit from the transfusion. In six cases there was jaundice of a mild grade which disappeared after a day or so. There was no tendency for the hemoglobin and red blood corpuscles to decline; generally they showed an elevation over the pretransfusion level. Leukocytosis was noted in several cases. During the interval of improvement, the outstanding untoward feature was continued oliguria which, in a number of cases, was associated with persistent nausea and vomiting.

The Delayed Reaction.—This was generally ushered in by symptoms of the central nervous system, of which agitation or drowsiness were the commonest. The symptoms began from a day or two to a week after the transfusion and progressed to a peak which was reached from the eighth to the twelfth day in the patients who recovered and from the fourth to the eighteenth day in the fatal cases. The outstanding observations were those usually associated with severe impairment of renal function, and belong to the syndrome commonly called uremia. In all cases in which the chemistry of the blood was studied there was considerable retention of nonprotein nitrogen and in one case, the carbon dioxide combining power of the plasma fell to 18.7 per cent by volume. The phthalein excretion in the two cases in which it was studied was markedly reduced. Edema was noted in five cases and was extreme in case 6. The blood pressure was definitely increased in cases 1, 4 and 15, but in several other cases in which it was followed there was no significant rise. Convulsions were observed in four cases and coma was noted in five cases. It is interesting that two of the five patients who became comatose

recovered. In three cases, there were definite purpuric phenomena at the peak of the reaction, and in a fourth case, frequent epistaxes were noted. In case 1, the purpura was associated with a fall in the platelet count.

The Outcome.—Six patients recovered and eleven died. In the patients who recovered, the peak of the reaction was reached from the eighth to twelfth day. In the fatal cases death occurred between the fourth and eighteenth day, with ten days as the average duration of life after transfusion. All eleven deaths occurred with uremic manifestations. Recovery was associated with considerable diuresis beginning at the peak of the reaction. Only in case 5 did recovery seem to result from any radical form of treatment; in this instance, decapsulation of the kidneys was performed. In several other cases, spontaneous recovery was as dramatic as the result in case 5. We cannot be sure that the decapsulation of the kidneys was responsible for the happy outcome.

SUMMARY OF AUTOPSY MATERIAL

Though nine of the seventeen cases (cases 3, 4, 7, 8, 11, 12, 15, 16 and 17) went to autopsy, the notes on the pathologic material of many of them are so brief that it is impossible to form any accurate judgment of the appearance of the various tissues. An attempt at tabulating such incomplete data might lead to erroneous conclusions. The abnormalities most frequently noted concern the liver and kidneys.

The liver of our patient showed central necroses; these were also present in cases 4, 8 and 16 and probably in case 7. The liver was not commented on in cases 11, 15 and 17; in case 12, there was a pre-existing nodular cirrhosis.

The changes in the kidneys were discussed at some length by all who reported on autopsies. Aside from the interstitial cellular infiltration, which was noted in six cases, and the dilatation of the glomerular capsules, which was noted in five, the striking abnormality seems to have occurred always in the tubules. Dilatation of the convoluted tubules was commented on in five cases and degenerative changes of some sort in the tubular epithelium were noted in every case. In all except case 4, the lumina of the tubules seem to have been filled with a peculiar material which was always scarce at the more proximal levels, but which was conspicuously abundant in the collecting tubules. In case 8, this substance was referred to as "masses" of hemoglobin; in case 11, as masses of brownish pigmented material; in cases 7 and 12, as masses and granules of eosin-staining material; in case 15, as masses, lumps and granules of an "isotropic substance of the color of brown sugar," and in cases 16 and 17 as yellowish-brown material. The most unusual feature of our case seems to have been the extreme degree of

epithelial necrosis. In none of the other cases was calcification noted, and in only one (case 17) was epithelial regeneration noted. Attention was not directed to the occurrence in the intact epithelial cells of droplets similar to the pigmented material found free in the tubular lumina. Yorke [26] gave an excellent description of exactly similar droplets in the renal epithelial cells (*a*) of dogs that died during the passage of hemoglobin resulting from infection with *Piroplasma canis* and (*b*) of rabbits four hours after the intravenous injection of hemoglobin. Yorke said of these droplets that there was "but little doubt that they are derived, in part, at least, from hemoglobin."

On the basis of our own observations at autopsy (case 3), which seem to agree in general with the observations of others, we feel justified in saying that the renal disease is of an unusual type. It is characterized chiefly by edema and cellular infiltration of the interstitial tissue, dilatation of the intracapsular spaces of the glomeruli, dilatation of the convoluted tubules, advanced necrotic changes in the tubular epithelium, especially that of the collecting tubules, with deposition of pigmented droplets in many of the cells and finally, the appearance in the tubular lumina of leukocytes, large phagocytic wandering cells, desquamated epithelium and peculiar pigmented globules of various sizes. Studies of the droplets in the epithelial cells and of the larger pigmented masses in the lumina of the tubules invite the suggestion that they are hemoglobin products of some sort. The droplets seen near the glomerular extremity of the tubule possess the staining characteristics of the hemoglobin that is contained in adjacent erythrocytes, but those which occur further down toward the renal pelvis have lost their eosinophilic and fuchsinophilic qualities and show increasing amounts of brownish pigmentation. Except for the occurrence of this pigment, the changes in the kidney are much like those found after poisoning with mercuric chloride. Hemorrhages into the mucous membranes were noted in four cases.

COMMENT

From personal study of the complete records of three cases and from the available information concerning fourteen others reported in the literature, we are led to believe that the characteristic delayed reaction following transfusion described here is dependent on the injection of incompatible blood.[27] Furthermore it would seem that most of the signs

26. Yorke, W.: The Passage of Haemoglobin through the Kidneys, Ann. Trop. Med. **5**:401, 1911.

27. It is important to note that Ottenberg and Johnson (Hitherto Undescribed Anomaly in Blood Groups, J. Immunol. **12**:35, 1926) found that the incompatible type of reaction may occur even when the donor and recipient are of the same blood group.

and symptoms by which the reaction may be recognized develop from the severe functional damage that the injected blood inflicts on the kidneys. That there is an adequate anatomic basis for this functional derangement is clearly shown in autopsy material from cases in which the reaction resulted fatally. When the descriptions are sufficiently detailed to permit analysis, one is struck by the similarity of the renal lesions in all cases: The kidneys are swollen, there are degenerative changes in the tubular epithelium and the tubules are filled with blood cells, desquamated epithelium, blood pigment and débris.

The observed facts seem simple enough: A person receives incompatible blood, as a result of which the kidneys are severely damaged and in due course of time uremia sets in. When we attempt to explain the mechanism by which the incompatible blood damages the kidneys, we find difficulty in arriving at a satisfactory conclusion. Four possible explanations are: 1. By mechanical blockage of their tubules, the kidneys have been rendered functionless as excretory organs. 2. The kidneys are sensitive to certain bodies contained in the injected blood, and the functional decline results from a local reaction which is of the nature of an anaphylactic shock. 3. The immediate transfusion reaction brings about a metabolic disturbance that affects renal function. 4. By the action of toxic substances set free in the blood at the time of transfusion, the functioning renal tissue is so severely damaged that it is unable to perform its duties. Each of these possibilities will be given brief consideration.

The conception that renal insufficiency following transfusion may be explained by mechanical blockage of the tubules dates back at least as far as Ponfik [3] who was among the first to observe blood pigment casts in the kidneys of dogs that had been given transfusions with incompatible blood. Those who support this view point to the fact that the urinary suppression dates from the outpouring of large quantities of hemoglobin in the urine. Thus far, however, there is no convincing proof of the fact that the casts found in the renal tubules during hemoglobinuria are responsible for the decline in urinary output. Nor indeed, is there sufficient evidence to say that hemoglobinuria per se alters in any way the function of the human kidney. It is apparently true that hemoglobinuria in rabbits (Lévy,[4] Yorke and Nauss,[28] Baker and Dodds [13] and others) may produce renal insufficiency with anatomic changes much like those described in human beings. Bayliss,[29] however, who studied the subject in other animals observed that injections of

28. Yorke, W., and Nauss, R. W.: The Mechanism of the Production of Suppression of Urine in Blackwater Fever, Ann. Trop. Med. **5**:287, 1911.

29. Bayliss, W. M.: Is Hæmolysed Blood Toxic? Brit. J. Exper. Path. **1**:1 (Feb.) 1920.

hemolyzed blood are "innocuous to the cat and dog." What is more significant, Sellards and Minot [30] injected sufficient quantities of hemoglobin into human beings to produce marked hemoglobinuria without appreciably affecting renal efficiency. It is noteworthy that in the latter experiments it seemed to make no difference whether the hemoglobin was derived from blood of the same or of an incompatible group. Dr. A. R. Rich,[31] who conducted similar investigations on human beings in the Johns Hopkins Hospital, arrived at the same conclusion: that the injection of hemoglobin in sufficient amounts to produce marked hemoglobinuria is a harmless procedure. Considering the matter from another point of view, it is significant that in several of the cases in which urinary suppression followed transfusion, hemoglobinuria was not noted. There is therefore no substantial reason for regarding the hemoglobinuria and the blood pigment casts as the direct cause of the renal insufficiency. Despite this, the histologic observations in the kidneys, previously described, make the theory still somewhat attractive.

The second possibility, that the kidneys are sensitive to a substance contained in the incompatible blood and that the renal insufficiency results from a reaction of the nature of an anaphylactic shock, finds its chief support in the associated clinical phenomena; the urinary suppression dates from a generalized reaction resembling anaphylactic shock. The fact that anaphylactic shock in the spontaneously hypersensitive person may be associated with a temporary but severe grade of renal insufficiency has been pointed out by Longcope and Rackemann.[32] After three days on a diet containing considerable beef, one of their patients who was markedly sensitive to beef serum suddenly had an attack of urticaria. Studies of renal function before, during and after the attack showed that during the attack there was marked albuminuria and cylindruria with retention of water, chlorides and nitrogen and a precipitate fall in phthalein excretion. It is conceivable that this reaction could occur in a person who is hypersensitive to the substances contained in incompatible blood.[33]

In discussing the third possibility, that the immediate transfusion reaction brings about a metabolic disturbance which affects renal function, we wish to consider particularly the salt metabolism. It is a well

30. Sellards, A. W. and Minot, G. R.: Injection of Haemoglobin in Man and Its Relation to Blood Destruction, with especial Reference to the Anaemias, J. M. Research **34**:469, 1916.

31. Rich, A. R.: Personal communication to the author.

32. Longcope, W. T., and Rackemann, F. M.: Severe Renal Insufficiency Associated with Attacks of Urticaria in Hypersensitive Individuals, J. Urol. **1**:351 (Aug.) 1917.

33. A more comprehensive discussion of this problem will be found in Lindau's article (footnote 5).

recognized fact that loss of chlorides as a result of persistent vomiting may be considerable. Associated with this loss of chlorides there is at times a remarkable nitrogen retention with clinical phenomena simulating the uremia of progressive renal disease. Bennett [34] has considered such conditions under the heading "Renal Disease of Gastric Origin." Whether there is actually a specific renal lesion accompanying the fall in chlorides is still an unsettled point. Brown, Eusterman, Hartman and Rowntree,[35] and Zeman, Friedman and Mann [36] described a severe grade of tubular nephritis in cases of pyloric obstruction in which persistent vomiting was followed by nitrogen retention and uremia. Blum and his associates in a great number of publications have recently contributed much to an understanding of this condition which they term "l'azotémie par manque de sel." They feel that the azotemia is not due primarily to a renal lesion, but that it is a compensatory mechanism resulting from loss of chlorides.[37] They describe the occurrence of this hypochloremic azotemia in a variety of conditions: (*a*) vomiting due to pyloric obstruction, (*b*) vomiting of unexplained origin,[38] (*c*) prolonged diarrhea,[39] (*d*) diabetic acidosis [40] and (*e*) nephritis with vomiting and restriction of the salt intake.[41] In going over our cases of transfusion, discussion arose as to whether we might be dealing with an azotémie par manque de sel. This was suggested by the facts that the nitrogen retention almost always followed a period of persistent vomiting, and that tetany—possibly gastric tentany—was described in two of the cases. It seems possible that loss of salt contributed to the symptomatology of some of the cases, but that it was not the most important factor seems clear to us from the following facts: (*a*) The edema that was present in a fair proportion of cases, and was extreme

34. Bennett, T. I.: Goulstonian Lectures on Some Problems of Nephritis (Lecture I), Lancet **1**:535 (March 17) 1928.

35. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction. Renal Insufficiency Complicating Gastric Tetany, Arch. Int. Med. **32**:425 (Sept.) 1923.

36. Zeman, F. D.; Friedman, W., and Mann, L. T.: Kidney Changes in Pyloric Obstruction, Proc. New York Path. Soc. **24**:41, 1924.

37. Blum, L.; Grabar, P., and van Caulaert, C.: L'azotémie par manque de sel. Son mécanisme. Ann. de méd. **25**:34 (Jan.) 1929.

38. Blum, L.; Grabar, P., and van Caulaert, C.: Phénomènes d'hypochloruration apparaissant chez un urémique traité par le régime sans sel, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:251 (Feb. 25) 1929.

39. Blum, L., and Weil, J.: Entérite aiguë avec état comateux et forte azotémie, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1620 (Dec. 6) 1928.

40. Blum, L.; Grabar, P., and van Caulaert, C.: L'azotémie par manque de sel dans le diabète grave, Ann. de méd. **25**:23 (Jan.) 1929.

41. Blum, L.; van Caulaert, C., and Grabar, P.: Les différents types de néphrites avec azotémie. Leur diagnostic differentiel, Presse méd. **37**:90 (Jan. 19) 1929.

in several, is not a feature of the hypochloremic azotemia. (*b*) In case 2, the only case in which the blood chlorides were adequately followed, there was no hypochloremia. The following tabulation shows the blood nonprotein nitrogen and blood chlorides (chloride as sodium chloride in the whole blood filtrate) in milligrams per hundred cubic centimeters in case 2:

	Feb. 2	Feb. 3	Feb. 7	Feb. 9	Feb. 13
Sodium chloride	532	532	548	564	577
Nonprotein nitrogen	147.8	150	60.3	46.2	32.4

The fourth possibility, that the anatomic and functional renal changes are brought about by irritating or toxic substances contained in the incompatible blood, is rendered plausible by the character of these renal changes. The edema of the kidney, the infiltration with wandering cells, and the necrotic tubular epithelium suggest an acute poisoning of some sort. Goormaghtigh,[6] in describing the kidneys of his patient (case 4), noted that they presented the picture of a toxic tubular nephritis. He considered the associated liver necroses as additional evidence for the theory that the whole reaction is due to a toxic process. The frequency with which liver necroses form a part of the pathologic picture is striking, and is a strong point in favor of this theory. Just what portion of the injected blood is capable of such toxic action it is difficult to say. Lévy,[4] who investigated this subject, came to the conclusion that the hemoglobin was the portion of the blood which damaged the tubular epithelium. Lévy's experiments however, were on rabbits and, as noted, more recent work seems to show that hemoglobin is innocuous to man. (In this connection it is interesting to note that in the descriptions of blackwater fever [Dudgeon [42]], one finds a picture similar to that of the transfusion reaction: a febrile paroxysm followed by hemoglobinuria, urinary suppression, vomiting, jaundice and, at autopsy, liver necroses and renal lesions not unlike those already described. As the patient recovers, the evidences of nephritis clear up rapidly. It is sometimes stated that the renal lesions of blackwater fever are due to the hemoglobinuria per se, but I can find no convincing proof of this. Lindau [5] commented at length on the similarity of the delayed transfusion reaction to blackwater fever. He also called attention to renal lesions in human paroxysmal hemoglobinuria and in the various hemoglobinurias of animals.) In short, though it cannot be said that any particular part of the incompatible blood is responsible, the changes in the kidney and liver are of such a character as to make tenable the conception that they are brought about by an irritating or toxic substance set free in the blood at the time of transfusion.

42. Dudgeon, L.: Blackwater Fever, J. Hygiene **19**:208 (Oct.) 1920.

Of course, it is difficult to say whether one or a combination of the foregoing possibilities accounts for the occurrence of uremia after transfusion. The fourth suggestion might explain the observations in the three cases that have come under our own observation, but as we have followed only three of the seventeen cases we hesitate to apply this explanation to the entire series. It has not been our purpose to explain; we wish rather to characterize what seems a clearly defined and probably not an uncommon type of reaction following transfusion.

Finally the fact should be emphasized that careful estimation of the daily output of urine will aid much in foretelling the ultimate outcome in these cases. It is well to remember that after an immediate reaction following transfusion the occurrence of the more dramatic hemoglobinuria is of far less prognostic significance than the amount of urinary excretion.

SUMMARY

1. A delayed or prolonged reaction following transfusion is described in seventeen cases. Of these cases, three are reported for the first time and fourteen have been gathered from the literature.

2. The reaction generally runs a peculiar and highly characteristic course which presents the following features: (*a*) Immediately after transfusion, there is a sharp febrile reaction, followed frequently by hemoglobinuria and invariably by suppression of urine. (*b*) There is an interval of several days during which there is symptomatic improvement but continued oliguria. (*c*) After this interval the characteristic features of the delayed reaction develop rapidly. They usually begin with agitation or drowsiness which is replaced by outspoken evidences of uremia. Convulsions and coma may supervene.

3. The outcome is frequently fatal; eleven of the seventeen patients died. Recovery is associated with diuresis; death occurs in uremia.

4. At autopsy the kidneys are swollen; the tubular epithelial cells contain droplets of a peculiar pigmented material and show advanced degenerative changes; the tubular lumina are filled with various cells, blood pigment and débris. Small necroses are generally found in the liver.

5. The events may be summarized as follows: A subject receives an injection of incompatible blood, his kidneys are severely damaged and in due course of time uremia sets in. Several possible explanations of these events are discussed.

6. The delayed reaction is not rare; beside the seventeen cases discussed in detail, a number of cases in the literature are cited.

THE MECHANISM OF THE EPIGASTRIC DISTRESS ASSOCIATED WITH AN IRRITABLE COLON AND CHRONIC APPENDICITIS *

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The epigastric distress due to extragastric lesions may so closely resemble that due to peptic ulcer that a detailed study is necessary for the differentiation. The present study is concerned with the mechanism of the epigastric distress associated with a spastic colon and chronic appendicitis. The fundamental factors responsible for the epigastric distress in these conditions are no doubt common to conditions caused by other extragastric lesions. Clinical observations [1] indicate that the discomfort is induced by a stimulation of the stomach. In a former investigation [2] a reflex stimulation of the stomach from the colon, appendix and gallbladder was demonstrated in the dog. The introduction of a few drops of croton oil in the proximal colon was usually followed by an increase in tone and a striking increase in the peristaltic action, particularly of the pyloric portion of the stomach. When the irritation was confined to the appendix or applied to the mucosa of the gallbladder, the same gastric phenomenon was observed. In each instance the stimulating effect on the stomach was promptly abolished by atropine.

These observations directed our attention to the study of the tone and peristaltic action of the pyloric section of the stomach in patients with a spastic condition of the colon and localized recurring epigastric distress. Patients were selected in whom it was possible to induce the typical epigastric distress by injecting air into the colon through a rectal tube. The quantity of air was measured and varied from a few cubic centimeters to 1,000 cc. Ordinarily, 500 cc. or less was effective. In some

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* From the Department of Internal Medicine, State University of Iowa.

1. Smith, Fred M.; Miller, G. H., and Fowler, W. M.: The Gastric Manifestations Associated with a Spastic Colon, J. A. M. A. **93**:1932 (Dec. 21) 1929.

2. Smith, Fred M., and Miller, G. H.: A Study of the Reflex Influence of the Colon, Appendix and Gallbladder on the Stomach, Arch. Int. Med. **46**:988 (Dec.) 1930.

instances the distress was produced by massaging an irritable section of the colon, particularly the ileocecal region. We were interested in the registration of the gastric activity of the pyloric portion of the stomach. A rubber condom was selected for this purpose. This was anchored in the pylorus by an Einhorn bucket which was attached to a piece of small rubber tubing, extending for from 3 to 4 inches (7.62 to 10.16 cm.) below the lower end of the condom. The position of the balloon was checked in several instances by fluoroscopic examination. After the balloon was passed into the stomach, the patient lay on the right side until it was engaged in the pyloric region. The balloon was then connected with the bellows recorder, and a control record of the gastric activity was obtained on the kymograph. Air was then introduced into the colon by means of a rubber bulb through a rectal tube. There was at once a striking increase in the tone, an onset of more active peristalsis and the appearance of the typical epigastric distress. The pain corresponded with changes in tone or the passage of a peristaltic wave.

REPORT OF CASE

The following report is indicative of the type of patient selected for investigation, and illustrates the method of study:

CASE 1.—F. W., aged 45, was admitted to the medical department of the University Hospital in July, 1929. He complained of recurring epigastric distress, which had been appearing at intervals over a period of ten years. The distress was localized slightly above and to the right of the umbilicus and was described as a feeling of fulness or a gnawing sensation. It appeared from one to three hours after meals and was more apt to follow the evening meal. There was frequently nausea and vomiting during severe distress, which was followed by complete relief. The discomfort was also relieved by belching and the passage of gas by bowel. The epigastric pain was often associated with distress, particularly in the right lower quadrant, and the consciousness of gas in the lower part of the abdomen. It was noticed that the pain was more apt to be present during periods of constipation, which were occasionally followed by diarrhea. The patient was more liable to have a severe attack of epigastric pain when the stools were scybalous. The gallbladder and appendix had been removed in 1925. Apparently neither of these structures had been significantly diseased. There was relative freedom from the discomfort for two and one-half years following the operation. During the months preceding admission to the hospital the distress was more severe and appeared at more frequent intervals. There was no history of hematemesis or melena.

Examination revealed tenderness in the right lower quadrant. The secretory function of the stomach was regarded as normal. Roentgen examination of the stomach gave negative results. There was a moderate spasticity of the colon. The introduction of air into the colon was followed by discomfort in the right lower quadrant and the appearance of typical epigastric distress.

A balloon was passed into the stomach and allowed to engage in the pyloric portion. It was then connected with a kymograph, and after a control record was obtained, air was introduced into the colon. Immediately following the injec-

tion of the air there was a change in tone, the stomach became active and the patient experienced the typical epigastric distress. The patient was taught to register the periods of distress. This distress corresponded with the peristaltic waves. It appeared during the upstroke and subsided on the downstroke. Following the administration of atropine, there was a gradual reduction in the tone of the stomach, and after a few minutes the peristaltic waves ceased and the pain disappeared. The gastric activity subsequent to the full effects of the atropine was similar to that during the control period.

A few days following the aforementioned experiment, a fluoroscopic examination of the stomach was again made. During the examination, air was introduced into the colon. The patient at once experienced distress. It was localized over the pylorus and occurred as a peristaltic wave passed over the pyloric ring. The distress in each instance disappeared as the wave passed and returned with the subsequent wave.

CASE 2.—The record in figure 1 is from another patient with a recurring localized distress, which occurred at from one and one-half to two hours after meals. Relief was obtained by taking soda, by belching, by the passage of gas by bowel and by bowel movement. This discomfort had appeared periodically for from four to five years and was more apt to be present during periods of constipation. In the gastro-intestinal examination, a spastic colon was the only significant observation. A rectal tube was passed, and as soon as air was introduced into the colon, the typical burning sensation was felt in the epigastrium. This distress was also induced by the massage of the ileocecal region, and the possibility of chronic appendicitis was considered. The internal inguinal rings were large, and a definite bulging was noted on coughing. The stretching of these rings by the fingers also produced the pain in the epigastrium.

In the gastric curve (fig. 1) there was a striking increase in tone, and the stomach at once became active. After the inflation of the colon the registration of the pain was done in the usual manner and is indicated below the gastric curve. The pain corresponded to the increase in tone or the passage of a peristaltic wave. In this experiment the influence of nitroglycerin was tested, and there was no apparent change following the first administration. After the second dose, however, there was a sharp reduction in tone and a decrease in the size of the peristaltic waves, but the epigastric distress continued. After a few minutes atropine was administered, with a subsequent reduction in tone, cessation of peristalsis and the disappearance of the pain.

These observations indicated marked changes in the stomach following the introduction of a small quantity of air into the colon. This feature was checked by a fluoroscopic examination. The position and activity of the stomach was carefully observed, and then air was injected into the colon. There was at once a striking increase in tone, and the stomach assumed a higher level and became active. A prepyloric spasm was noted, and the typical pain was localized over this area. This pain was intermittent and continued to be localized over the spasm, regardless of the change in the position of this region of the stomach.

The patient was transferred to the department of surgery for the repair of the hernia and removal of the appendix. There was, however, no significant pathologic process in the appendix.

The following case is of particular interest because of the delayed response to the injection of air into the colon.

CASE 3.—This patient was well until five months prior to examination in December, 1929. He began to notice a gnawing pain in the epigastrium that

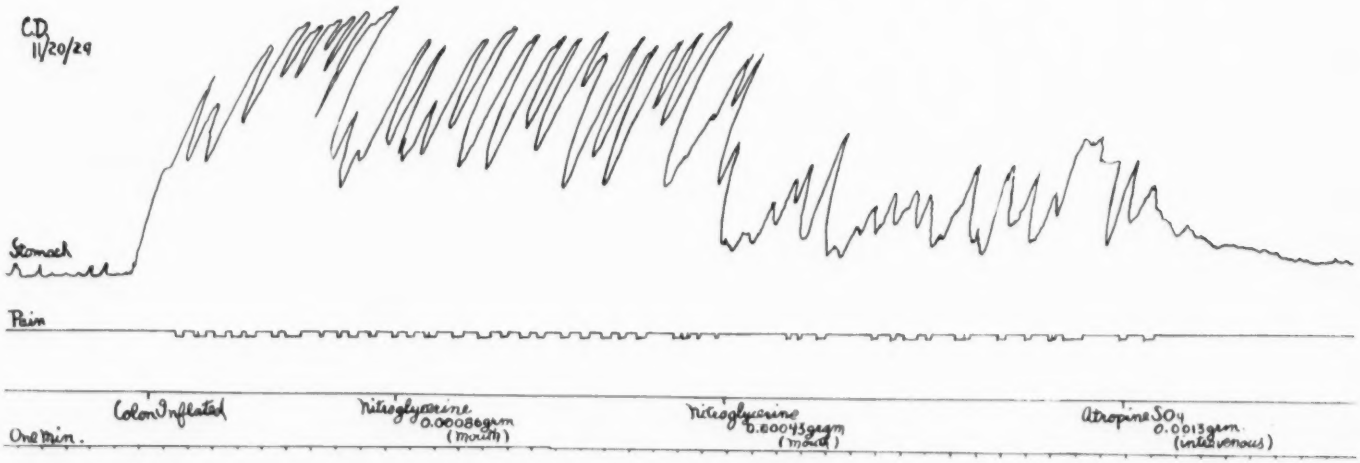

Fig. 1.—The appearance of pain is recorded on the line below the gastric curve. Each registration of the time marker represents one minute. The introduction of air into the colon was followed by an increase in tone, the onset of an active peristalsis and the appearance of the epigastric distress. In each instance the occurrence of the pain corresponded with a peristaltic wave or a change in tone. The stimulation effect on the stomach was diminished by the second administration of nitroglycerin and later abolished by the administration of atropine.

occurred two to three hours after meals. This distress was relieved by the taking of food and soda. There was an occasional sensation of pressure throughout the entire abdomen. The bowels were inclined to be constipated, and since the onset of the illness the stools were frequently scybalous. It was during this period that the distress was most frequently experienced in the epigastrium. On the other hand, if the stools were formed and of good size, there was relative freedom from the pain. The free acid of the gastric content was relatively low. Roentgenologic examination of the stomach showed a prepyloric spasm, but no evidence of ulcer.

After the registration of a control period of the gastric activity, air was introduced into the colon in quantities of 500 cc., on two occasions, without any apparent alteration in the stomach and without pain (fig. 2). Within a few minutes the patient began to experience discomfort over the lower part of the abdomen, with an intense desire to move the bowels. Coincidentally there was an abrupt increase in the tone of the stomach, the registration of tall gastric waves and the appearance of the typical epigastric pain. Later, air was expelled, which was followed by relief from the lower abdominal discomfort, but the epigastric distress continued. In the meantime there was some reduction in the gastric activity. Atropine was then administered, with a subsequent reduction in gastric tone, a cessation of peristalsis and the disappearance of the epigastric pain.

Later, another fluoroscopic examination of the stomach was made and air was introduced into the colon. Coincident with the injection of the air a marked prepyloric spasm was observed, and the typical pain was produced which was localized over the spasm.

The localized epigastric pain associated with a spastic colon could occasionally be induced by palpation of the ileocecal region.

The curve in figure 3 illustrates this feature. The registration on the line below the gastric curve indicates the time when the cecum was massaged. It will be noted that there was a gradual increase in the gastric tone, and the peristaltic waves became more prominent. This alteration in the stomach persisted for a few minutes after the irritation of the cecum was discontinued. Immediately following the initial massage of the cecum a sensation of fulness was felt in the epigastrium. Later, coincident with the large waves, the typical epigastric distress appeared.

The observations on a patient with chronic appendicitis were almost similar to those previously recorded.

Case 4.—A woman noticed a gnawing distress in the epigastrium in February, 1923, about three weeks following the birth of her third child. This distress was located slightly to the right of the midline and above the umbilicus, and usually occurred from two to three hours after meals. It appeared at infrequent intervals, and did not cause any inconvenience until 1925, following the birth of the fourth child. On the fourth day after delivery she had fever, diarrhea and generalized abdominal distress. Two weeks later, on her first day out of bed, she had a severe attack of episgatric pain that extended to the back. After a few minutes the pain was transmitted to the right lower quadrant. Following this severe attack the gnawing pain in the epigastrium occurred at more frequent intervals and was often associated with distress over the lower part of the abdomen, particularly on the right side. Physical examination disclosed considerable tenderness in the right lower quadrant over the region of the appendix. On palpation of the region, the typical epigastric distress was induced. The gastric

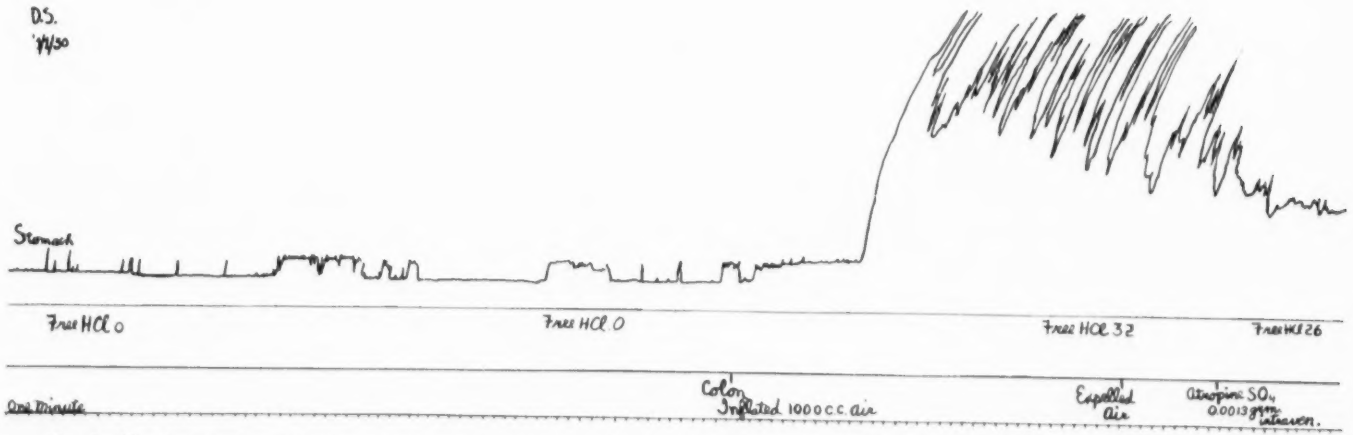

Fig. 2.—The introduction of 500 cc. of air on two occasions had no immediate influence on the gastric activity. A few minutes later, however, the patient began to have discomfort over the lower part of the abdomen and a desire to move the bowels. There was an abrupt change in the gastric activity, and the epigastric distress appeared again. This distress corresponded with the peristaltic waves. The usual response to atropine was noted.

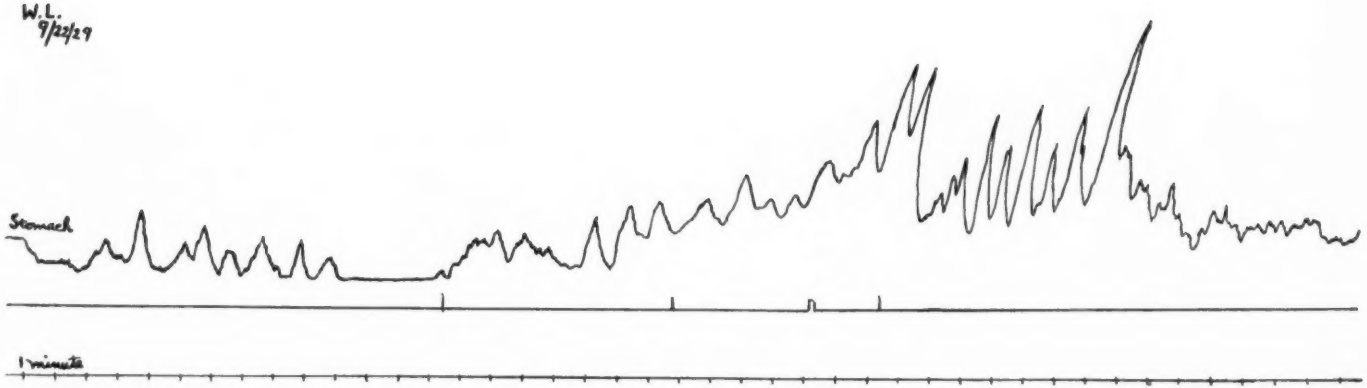

Fig. 3.—This illustration shows the stimulating effect on the stomach induced by massaging the ileocecal region. The registration on the line below the gastric curve indicates the time of the massage.

acidity was regarded as normal. Roentgenologic examination of the stomach showed a prepyloric spasm, but no evidence of ulcer. The appendix was visualized during the fluoroscopic examination, and was tender on palpation.

It is to be noted in the gastric curve (fig. 4) that pressure over the region of the appendix induced a striking increase in the tone and the peristaltic action of the stomach. Coincident with this change in the stomach, the gnawing epigastric pain was felt. After the administration of atropine the curve returned to that of the control period, and the distress disappeared. The inflation of the colon elevated the registration lever, but no other change was noted, and the distress was not induced. In a later experiment the injection of air into the colon produced changes in the stomach similar to that induced by palpating the appendix which were also accompanied by distress. There was a prompt response to atropine, even though the air remained in the colon, and subsequent pressure over the appendix had no significant effect.

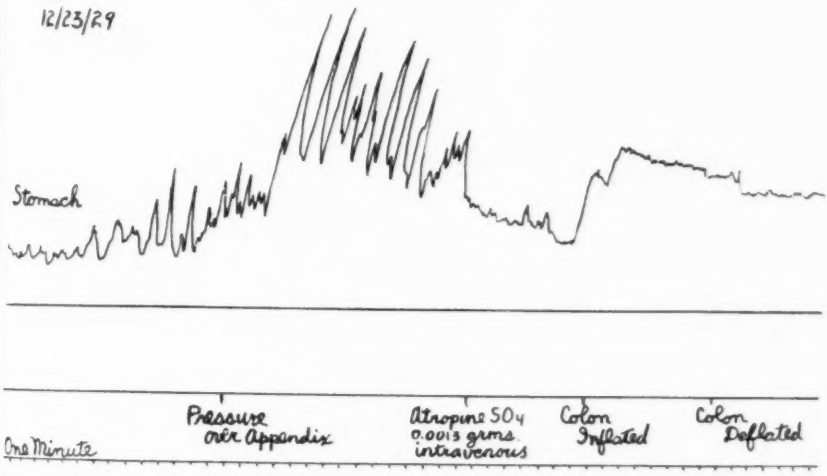

Fig. 4.—Record of patient with chronic appendicitis. Note the effect of pressure over the appendix. The epigastric distress was induced by the pressure, and corresponded with the peristaltic waves. Following the administration of atropine, the introduction of air into the colon caused some elevation of the writing lever, but had no significant influence in gastric activity.

This patient was later studied by the fluoroscope. The stomach was carefully observed, and then the appendical region was massaged. The tone of the stomach was increased, a prepyloric spasm was noted, and the epigastric pain appeared. It is to be observed that the position of the stomach was changed (fig. 5). Air was then injected into the colon. There was a striking change in the position and shape of the stomach; the prepyloric spasm was more evident, and the pain became intense. The pain was localized over the spasm (fig. 5*C*). A picture was taken during pain, and shows the extent of the spasm (fig. 5*D*).

It was felt that possibly a continuous curve of the gastric activity might contribute to the explanation of the periodicity of the epigastric pain. A continuous

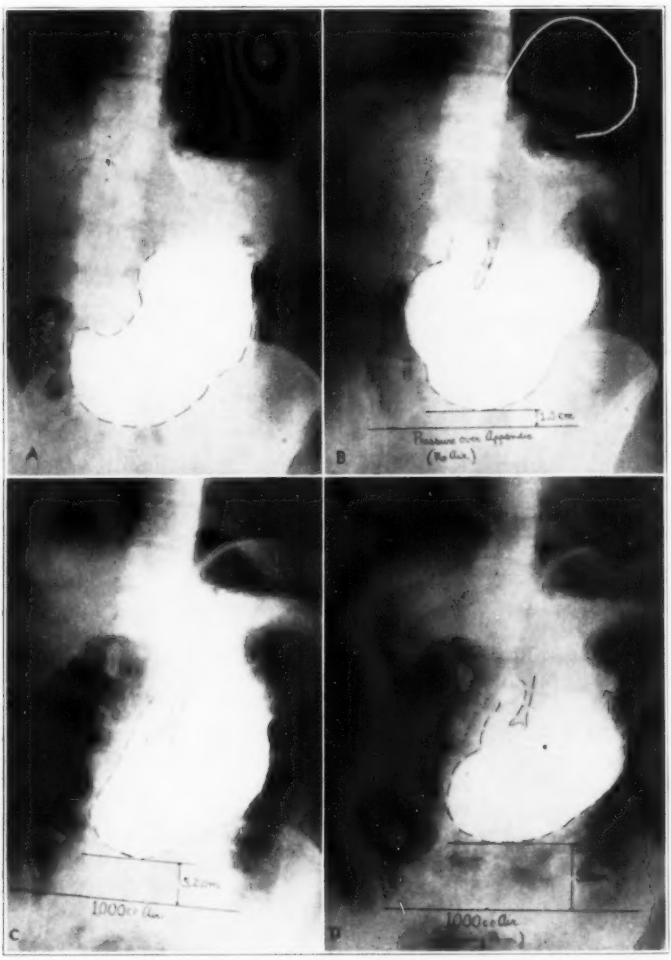

Fig. 5.—*A*, control roentgenogram; *B*, after pressure was applied over the appendix; C, after the introduction of air into colon; note the pyloric spasm; *D*, roentgenogram taken during pain. There was a further elevation of the stomach and the pyloric spasm was more marked. The pain was intense and localized over the region of spasm.

curve was recorded from 8:15 in the morning until 2:15 in the afternoon. The stomach was relatively inactive until about 11:30, and the patient was free from discomfort. There was then a gradual increase in the frequency and depth of the peristaltic waves until 12:30, followed by an abrupt cessation of peristalsis. During the height of the increased peristalsis the gnawing distress was felt in the epigastrium. The pain disappeared with the last large peristaltic wave. About one hour later the cycle was repeated in a minor form. The periods of active peristalsis were regarded as hunger contractions and believed to be related to the production of the pain.

This patient was operated on, and a chronically infected appendix was removed. The diagnosis was later confirmed by the pathologist.

In certain instances of gastric and duodenal ulcers there is a reflex stimulation of the stomach from the colon which contributes to the production of the epigastric pain.

CASE 5.—The curve in figure 6 was taken from a patient with recurring duodenal ulcer. The diagnosis of ulcer was first made in 1925. Treatment was instituted in a hospital for two months, and the distress disappeared. The patient was free from symptoms until July, 1929. When the patient was admitted to the University Hospital on Oct. 14, 1929, the clinical and roentgenologic observations were those of a duodenal ulcer. In the beginning of the gastric curve there was active peristalsis, and the typical epigastric pain was felt with each wave. Following the introduction of 30 cc. of a 2 per cent solution of sodium hydroxide into the stomach, there was a cessation of the peristaltic waves, and the pain disappeared. Later, air was injected into the colon with a subsequent increase in pain, and, finally, violent changes in the tone, which were accompanied by severe epigastric pain. Amyl nitrite was administered on two occasions without any appreciable influence on the gastric activity or pain. The administration of atropine, however, was followed by a prompt disappearance of the changes in tone and the cessation of pain. The patient stated that the distress induced by the injection of air into the colon was identical with that experienced in the past.

In the majority of the cases of peptic ulcer so far studied, there was no demonstrable stimulation of the stomach from the colon, and the introduction of air into the colon did not induce the epigastric distress. This feature was illustrated in several patients, and in each instance the colon was distended to the point where the patient was exceedingly uncomfortable, yet there was no change in the curve, nor was there epigastric pain.

COMMENT

In the present investigation, a reflex stimulation of the stomach from the colon and the appendix was demonstrated in patients with an irritable colon, chronic appendicitis and peptic ulcer. The stimulating effect on the stomach was manifested by a striking increase in the tone, particularly of the pyloric portion, and an increase in the peristaltic action. The same results were obtained regardless of whether air was injected into the colon or the ileocecal region was massaged. In all except one instance, the gastric response was prompt. In this patient

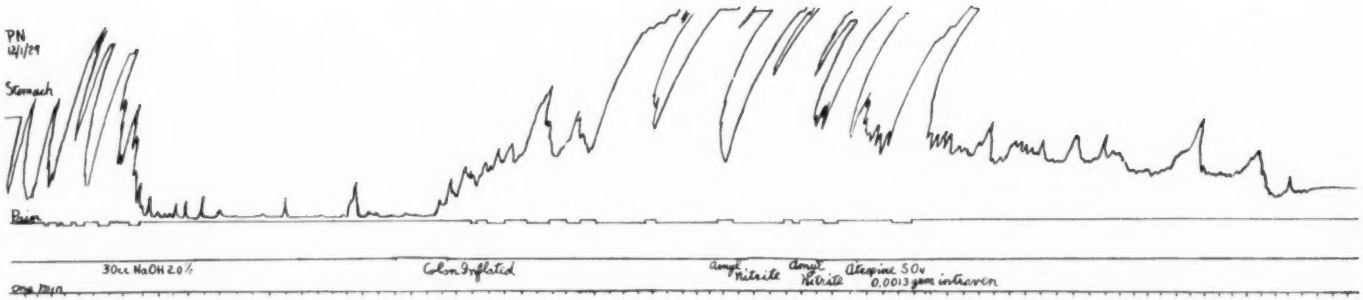

Fig. 6.—Record taken during treatment for duodenal ulcer. During the early period of this record the patient was experiencing the typical epigastric distress which is registered below the gastric curve. Note the effect of sodium hydroxide. Later the colon was stimulated by the introduction of air. A change was at once noted in the gastric curve. The patient again felt an epigastric distress, which he stated was like that experienced in the beginning of the experiment. This pain was again definitely related to the gastric activity. The stimulation of the stomach was eliminated by atropine, and the pain disappeared. Amyl nitrite had no effect.

the introduction of 500 cc. of air into the colon on two occasions had no significant influence on the tone or peristaltic action of the stomach. Later, however, when the patient began to experience severe cramps over the lower part of the abdomen, there was an abrupt change in the stomach with the appearance of the typical epigastric distress. The stimulation was apparently not sufficient until the onset of violent peristaltic waves in the colon. The observations in the roentgenologic examination were in accordance with the kymographic records. Alteration in shape and position and frequent marked prepyloric spasm were noted. The results from the kymographic study were more striking, which might be expected from the more delicate means of registration.

Coincident with the onset of the induced alteration in the stomach, the typical localized epigastric distress appeared. In each instance the distress corresponded with changes in tone, or with the passage of a peristaltic wave over the pyloric portion of the stomach. This distress was usually intermittent, and during active peristalsis it appeared on the upstroke of the lever and subsided on the downstroke. In those instances in which tone changes were the striking feature, the distress persisted until the spasm relaxed. Marked change in tone alone was apparently sufficient to produce the pain, but peristaltic waves, regardless of their intensity, did not seem to be so effective unless opposed by an increase in tone or a spasm of the pylorus. The fluoroscopic observations corresponded with those of the kymograph. The distress was localized over the pylorus, and the external location changed with the shifting of that portion of the stomach. The intermittent pain appeared as the peristaltic wave approached the pylorus, and persisted until the barium sulphate was expelled through the pyloric sphincter. One could predict with a considerable degree of accuracy the exact time of onset and of cessation of the pain. The intensity of the pain seemed to vary with the degree of spasm, and in some instances it was intense. In those instances in which epigastric pain was not induced by the stimulation of the colon, no significant changes were demonstrated in the stomach by either the kymograph or the roentgenologic study.

In the kymographic study the gastric alteration induced by the stimulation of the colon usually subsided after the tension in the bowel was reduced by the expelling of air through the rectum, or was abolished by atropine, even though the air remained in the colon. Amyl nitrite and nitroglycerin were employed in some instances, but they were much less effective than the atropine.

These observations indicate that the epigastric distress of a spastic condition of the colon and chronic appendicitis is gastric in origin, and that it is induced by a reflex stimulation of the stomach. This distress may appear at any time that there is sufficient stimulation of the stomach.

It may occur immediately after meals, particularly when the colon is irritable. There may thus be considerable variation in the time of occurrence, which is one of the features that differentiates this type of pain from that of peptic ulcer. Frequently, however, the distress has a definite periodicity that apparently corresponds with the appearance of hunger contractions. The tone and peristaltic action of the stomach is ordinarily greatest at this time. If the tone of the pyloric portion of the stomach is further increased by a stimulation from the colon or the appendix, the epigastric distress appears.

The gastric pain associated with chronic appendicitis and irritable colon may be identical with that caused by peptic ulcer. This type of pain is not dependent on an ulceration of the stomach, nor is it possible for the hydrochloric acid of the gastric content to be a factor. In fact, the free hydrochloric acid is inclined to be low or even absent. The pain induced in patients with peptic ulcer by the stimulation of the colon was said to be identical with that of distress caused by the ulcer. The gastric alterations strikingly resembled those accompanying an irritable colon and chronic appendicitis. The pain also occurred under the same conditions. It would thus seem that the changes in the stomach responsible for the pain in the former condition are probably fundamental in the production of pain in peptic ulcer. A study of the gastric alterations associated with peptic ulcer is in progress and will be reported in a later communication.

CONCLUSIONS

The recurring localized epigastric distress associated with an irritable colon or chronic appendicitis is gastric in origin and is induced by a reflex stimulation of the stomach. The stimulation of the stomach is manifested by an increase in tone, particularly of the pyloric region, and an increase in the peristaltic action. The pain appears to be coincidental with the change in tone and the passage of a peristaltic wave over the pyloric portion of the stomach. The distress may be induced any time at which there is sufficient stimulation of the stomach. It may thus occur immediately after meals or at irregular intervals, but frequently a definite periodicity is observed which corresponds with the appearance of hunger contractions.

In certain instances of peptic ulcer a reflex stimulation of the stomach from the colon was demonstrated, and the typical epigastric distress was induced. The gastric alterations strikingly resembled those associated with irritable colon or chronic appendicitis, and the pain occurred under the same conditions.

In those instances in which epigastric distress was not induced by a stimulation of the colon, no significant changes were demonstrated in the stomach.

ACROMEGALY WITH DIABETES MELLITUS AND XANTHOMA DIABETICORUM

REPORT OF A CASE *

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NEW YORK

That a decreased carbohydrate tolerance accompanies acromegaly was conclusively shown by Davidoff and Cushing.[1] In view of their observations it is not surprising to find the incidence of diabetes mellitus high in this condition. John [2] reported three cases of this kind, in two of which the onset of acromegaly preceded the onset of diabetes. The fact that pituitary extract has an antagonistic action to insulin [3] has brought up the question of whether the diabetes is a true diabetes or the result of an interference with the normal action of insulin. In some cases it would seem that there is a relative, rather than a true, pancreatic deficiency. In others, however, there is little doubt that the diabetes is a true diabetes mellitus, the acromegaly possibly being the original factor in causing the diabetes. Joslin [4] pointed out that the chromophilic cells of the pituitary exert a partially controlling influence on the cells of the islands of Langerhans, and that in hyperpituitarism the former are increased in number.

The occurrence of xanthoma diabeticorum in severe cases of diabetes was reported by several observers. Outstanding among these was a review of seventy-four cases by Major [5] in 1924. The tumors are most numerous on the flexor surfaces of the forearms and legs. With this complication there is severe lipemia and a high content of cholesterol in the blood. Major expressed the belief that the disappearance of the tumors is due to the decrease of lipemia and hypercholesteremia. Pathologically, the tumors show fibrosis with an infiltration of small mononuclear leukocytes. The nodules are composed of neutral fat, fatty

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1. Davidoff, L. M., and Cushing, H.: Studies in Acromegaly: Basal Metabolism, Arch. Int. Med. **39**:673 (May) 1927.

2. John, H. J.: Possible Relationship Between Acromegaly and Diabetes, Arch. Int. Med. **37**:489 (April) 1926.

3. Burn, J. H.: J. Physiol. **57**:318, 1923.

4. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928.

5. Major: Bull. Johns Hopkins Hosp. **35**:27, 1924.

acids and lipoid bodies and contain cholesterol. Goldstein and Harris [6] described the involution of these tumors after six weeks in a patient whom they observed. There was a marked flattening of the nodules with loss of color, but the total number did not decrease markedly.

The patient in the following case had acromegaly and severe diabetes with xanthoma diabeticorum. The acromegaly had persisted since adolescence and had apparently preceded the onset of the diabetes.

REPORT OF CASE

An Italian, 37 years of age, was admitted to the hospital on Feb. 11, 1930, with the chief complaints of weakness and papules over the whole body. The family

Fig. 1.—The distribution of the tumors on the forearms and the acromegalic character of the hands.

history was difficult to obtain, but the patient said that his brother had the same facies. The symptoms of polyuria, polydipsia and loss of weight dated back to March, 1929, at which time the patient noted small pinkish tumors on both arms and forearms. The patient said that he had felt weaker since the onset and that this weakness had become progressively worse. The tumors increased somewhat in size, and he went to a hospital for treatment. He was placed on a diet and the tumors disappeared. After his discharge from the hospital, however, the tumors reappeared in greater numbers than previously and persisted up to the time of his admission to Bellevue hospital.

Physical examination revealed obvious acromegaly (figs. 1, 2 and 3). There was an acetone odor to the breath. The eyeballs were normal. Examination of the chest

6. Goldstein and Harris: Am. J. M. Sc. **73**:195, 1927.

Fig. 2.—The distribution of the tumors on the knees.

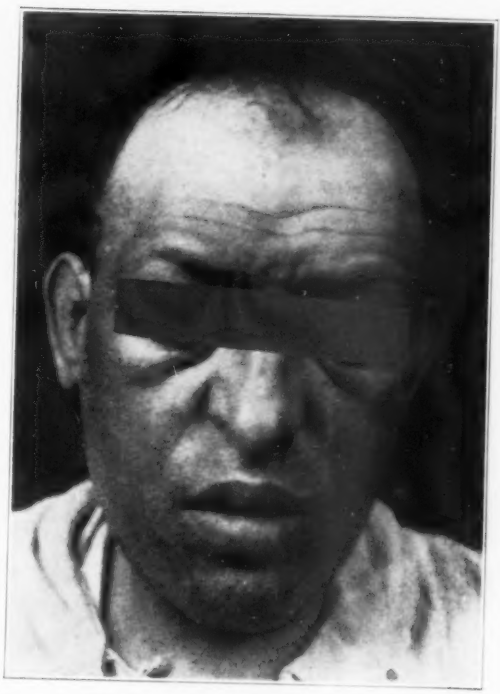

Fig. 3.—The acromegalic facies.

gave negative results. The heart was slightly enlarged, and there were no murmurs. On the outer aspect of both arms, from the wrist to just below the shoulder, but more numerous over the forearms and elbows, there were small tumors varying in size from 0.2 to 0.5 mm. They were also seen over the knees. The growths were firm and yellowish pink. They were not tender or painful. For the most part they were discrete, but over the elbows and knees they tended to coalesce.

Laboratory Observations.—The first twenty-four hour specimen of urine showed 48 Gm. of sugar, 3+ acetone and 2+ diacetic acid. The blood sugar

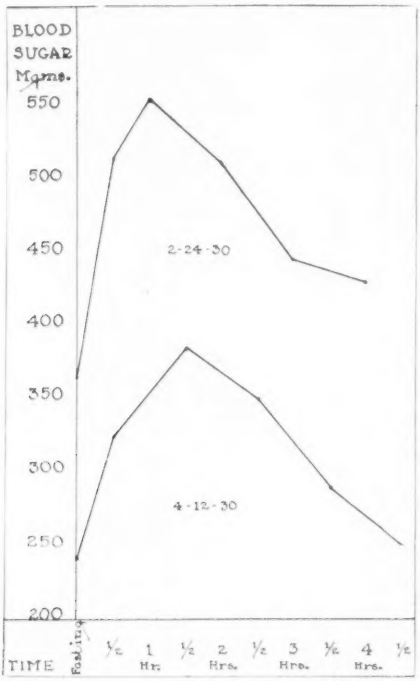

Fig. 4.—Dextrose tolerance curves obtained on Feb. 24 and April 12, 1930.

content was 250 mg. The patient was placed on a diet of carbohydate, 112 Gm.; protein, 62 Gm.; fat, 127 mg., and a total dose of 35 units of insulin daily. This had practically no effect on the output of sugar, and the urine continued to show sugar for seven days. The insulin was increased to 45 units during this time, but apparently the patient was having food brought to him from outside the hospital. In an effort to gain his cooperation, the carbohydrate in the diet was raised to 140 Gm., the protein and fat remaining the same. At this time the blood sugar content was 300 mg., and the output of sugar 38 Gm. a day. The acetone and diacetic acid had disappeared. The insulin was again increased, this time to 70 units, and the patient became sugar-free. The urine still showed sugar occasionally, but the

blood sugar during fasting was considerably lower. Except on two occasions, it remained below 200 mg. after glycosuria was controlled. When glycosuria reappeared, the intake of insulin was raised until the condition disappeared again. In this way the patient was kept fairly well under control.

The first estimation of blood cholesterol was made when the blood sugar was at a level of 300 mg., and when there was an average of 40 Gm. of sugar daily in the urine. The serum was milky white and typical of extreme lipemia. The cholesterol content of the blood at this time was 5,900 mg. This was determined by the Sackett [7] method, which is a modification of the Bloor method. It was checked and found to be correct. In reporting the comparative results of cholesterol determinations made by the Sackett method and the Bloor method, Sackett found that the original Bloor method gives a somewhat higher reading. In the university laboratories the normal cholesterol content of the blood, as determined by the Sackett method, was found to average 175 mg. The cholesterol reading for this patient was so high as to deserve mention. After the patient had been sugar-free for two weeks it was found to be 450 mg.; at this time the blood serum was normal, and it remained so. The cholesterol was determined on two more occasions, and again was found to be 450 mg.; on a third occasion it was 385 mg. The blood sugar at this time was 174 mg. One of the tumors was excised on March 22, at which time the blood cholesterol was 450 mg. This tumor was extracted for cholesterol. The total weight of the sample was 10 mg. and it contained 0.8 mg. of cholesterol. This determination was also made by the Sackett method.

Two blood sugar curves were obtained: one on February 24 and one on April 12. On both occasions the patient was given 100 Gm. of dextrose by mouth. The readings, in milligrams, are as follows:

February 24		April 12	
Fasting	364	Fasting	241
½ hour	526	½ hour	327
1 hour	556	1½ hours	384
2 hours	513	2½ hours	350
3 hours	444	3½ hours	289
4 hours	430	4½ hours	250

These curves obviously point to a severe form of diabetes. The phenolsulphonphthalein test showed a normal kidney function, the total output over a two hour period being 72 per cent.

The urea clearance test for kidney function, according to the method of Möller, MacIntosh and Van Slyke,[8] gave the following results:

	1st hour	2d hour
U/B ratio*	36.63	43.1
Standard clearance	49.67 cc.	57.67 cc.
Per cent of normal	91.89	106.7

* Urine urea nitrogen / Blood urea nitrogen

This showed that there was no impairment of kidney function.

Dr. I. J. Landsman furnished the following roentgen report: The hands showed changes characteristic of acromegaly. Roentgenograms of the skull showed

7. Sackett: J. Biol. Chem. **44**:203, 1925.

8. Möller; MacIntosh, and Van Slyke: J. Clin. Investigation **6**:427, 1928.

Fig. 5.—Roentgenogram showing the increased size of the sella turcica and the erosion of the anterior and posterior clinoids.

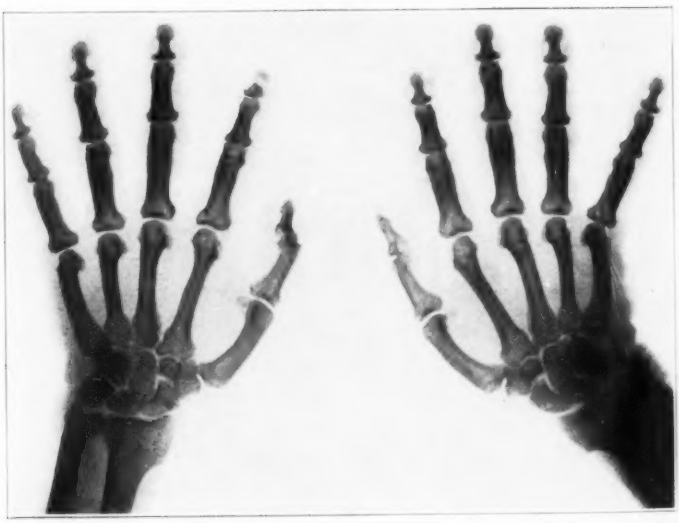

Fig. 6.—Bones of the hands showing changes characteristic of acromegaly.

the sella turcica increased in size, the maximum anterior posterior diameter equal to 20 mm. and the height equal to 16 mm. There was definite erosion of the anterior and posterior clinoids. The observations were considered characteristic of a pituitary neoplasm with acromegalic changes.

The photograph of the arms and hands of the patient (fig. 1) shows the arrangement of the tumors and the acromegaly of the hand. The tumors are also seen in the photograph of the knees (fig. 2), and the acromegalic facies is well demonstrated in the photograph of the patient's head (fig. 3). During his stay in the hospital, the tumors were much reduced in size and number but did not entirely disappear. They were distinctly flatter, some being almost flush with the skin. Where they had disappeared, there remained a slight brownish scar.

COMMENT

In view of the fact that the patient had marked acromegaly and showed a definite tumor of the pituitary gland, the severity of the diabetes is not surprising. The hypercholesteremia and lipemia responded well to insulin and diet, but in spite of this the tumors regressed slowly. The difficulty in keeping the patient continuously sugar-free, even with fairly large doses of insulin, may be accounted for by the increased activity of the pituitary gland. There seems to be little doubt that in this case the diabetes was a true diabetes mellitus, a fact attested to by the presence of the xanthoma, the hypercholesteremia and the high blood sugar curves.

Book Reviews

A Practical Medical Dictionary. By Dr. Thomas Lathrop Stedman. Eleventh, revised edition. Price, $7.50. New York: William Wood & Company, 1930.

This eleventh edition of Stedman's "Medical Dictionary" is of a convenient size and adequately fulfills the requirements of such a book. The primary value of any dictionary, medical or otherwise, is determined in large measure by the author's ability to construct definitions that will be both accurate and concise. In dictionaries of this type one does not expect or desire to find detailed explanations. The author of this work did not lose sight of this fact, and his definitions are well framed and to the point.

Certain devices are introduced which deserve a word of comment because they are the means of conserving time and effort on the part of the inquirer. 1. The definitions are so lucid that a person with little or no medical knowledge is able to understand the meanings at first reading. This quality is of especial importance to students or assistants to physicians. 2. Certain processes, conditions and objects are illustrated, frequently in color. 3. So far as possible, the author has omitted the long lists in the general body of the dictionary. When it has been found necessary to insert such lists, they have been reduced to a minimum by merely giving a name and following this with an asterik indicating that under the qualifying word the reader will find a more complete description. For example, under the list entitled "test" one finds "Widal's * Test." The reader may then find this word in its proper alphabetical order, and in addition to a description of the test, the author has been able to include some biographical data. Had all this information been given in the list it would have interrupted the alphabetical sequence and proved extremely cumbersome. 4. In some cases the author has inserted under the English titles lists in small type which furnish scientific data about the various conditions associated with the parts.

The etymology of the words used in medicine and the formation of terms are compact and clear. The sources of the words are given; Greek sources are given in Roman letters. The author makes the statement that this is done because Greek is no longer generally studied by physicians, as it was in the past. The following example indicates the manner in which this phase is handled: Macrocyte (G. makros, large, + kytos, cell). The more simple spelling of medical terms has been given preference; the old spellings are given as alternatives.

The appendix furnishes data concerning doses and uses of drugs, weights and measures, stethoscopic abbreviations, temperature and barometer scales, chemical elements and pathogenic microparasites.

On the whole, Stedman's "Medical Dictionary" impresses one as being a highly useful and convenient reference book both for physicians and for laymen who have an interest in medicine.

Les syndromes douloureux de la région épigastrique. By Rene A. Gutmann, Ancien interne des Hôpitaux de Paris, Attache medical de la clinique chirurgicale de la Salpétrière, charge des consultations des maladies du foie et du tube digestif. Volumes 1 and 2. Price, 200 francs. Pp. 1093, with 344 roentgenograms and 198 schematic drawings. Paris: Gaston Doin.

The first volume, covering 520 pages, begins with a general discussion of the symptom, epigastric pain. It then presents the various syndromes and clinical forms of ulcer. Special chapters are devoted to duodenal ulcer, gastric ulcer and juxtapyloric ulcer. Under each of these headings, the clinical picture, together with a detailed description of the roentgen appearance, is given. A chapter on

the treatment for ulcer follows. Gastric carcinoma is dealt with fully, including lymphogranulomatosis, sarcoma and benign tumors of the stomach. The clinical picture, the roentgenologic aspect and the treatment for disease of the gallbladder are similarly set forth.

The second volume begins with a description of the perivisceral syndrome, which is said to be the same for all conditions occurring in the upper part of the abdomen. Pyloric and duodenal stenosis and pyloric insufficiency are next considered. Two hundred pages are devoted to ptosis and dyspepsia, under which are described hyposthenic, orthostatic, hepatic, pancreatic, renal and other even less tangible syndromes. The epigastric distress seen in syphilis and tuberculosis, together with a good description of the organic diseases produced in the upper part of the abdomen by these two infections, is included. The volume ends with a good account of gastrojejunal ulcer, its symptomatology, roentgenologic manifestations, etiology, complications and treatment.

In general, it may be said that the work is thorough. The clinical phases are well presented, being divided into the almost multitudinous forms and syndromes so frequently found in the French literature. The x-ray sections, well illustrated with excellent plates and sketches, are commendable. Very little can be said, however, for the sections on therapy or for the ones dealing with ptosis, kinks, bands, adhesions and dyspepsia. The work is thorough, but frequently not critical.

History of Haitian Medicine. By Robert P. Parsons, Lieut. Com., M.C., U.S.N. With a Foreword by Edward R. Stitt, Rear Admiral, M.C., U.S.N. Price, $2.25. Pp. 196, with illustrations. New York: Paul B. Hoeber, Inc., 1930.

This is a highly interesting account of disease in our neighboring Negro-ruled sovereign state of Haiti and the dramatic medical development with the American occupation. So much has been written on the seamy side of Haitian politics and so many aspersions have been cast on this country's efforts by certain factions of the public press that it is refreshing to read of the indisputable achievements of the enthusiastic and scientific medical personnel of the United States Marine Corps and the later organized Public Health Service. The story falls naturally into two parts, Haitian medicine before the American occupation and that following this event in 1915. For centuries after the landing of Columbus in December, 1492, the island remained a plague spot of the earth. A cited author writes that the nosology of Haiti in 1804 would include all the diseases that 312 years of European intercourse would contribute to what the Caribs left before their extermination, together with all that Africa could add in 292 years of slave trade. Smallpox, yellow fever, malaria, yaws, tetanus, voodooism and revolution made life precarious. Yet the population grew. It may be surprising, but it was yaws and not the better known tropical diseases which constituted the major medical problem at the time of the American occupation. This was apparently first appreciated by Dr. Paul W. Wilson of the Public Health Service, who "poured arsenicals into the seething black mass and saw yaws lesions fade away, not in individual cases, but from a whole mountain side." The author holds to the view generally accepted by the medical corps of the military services that yaws is a modified form of syphilis. The style is simple and pleasant, and the volume maintains the high standard of Hoeber's series of books on medical history.

Anatomy. By George W. Corner. Price, $1.50. Pp. 82, with 8 illustrations. New York: Paul B. Hoeber, Inc.

This book presents in a most scholarly and delightful form a brief review of the development of the science of anatomy from the earliest times. It is one of a series of primers on the history of medicine published by Hoeber under the general title "Clio Medica." On account of the brevity imposed by the plan, only the most fundamental concepts, discoveries and methods are reviewed. Dr. Corner

has selected these with admirable judgment, and has presented them with a clearness which enables the reader to appreciate their significance. At the end is a brief chapter on current trends in anatomy which indicates the lines along which anatomy is contributing to the advance of the science of human biology.

The trend is toward the study of living tissues from a dynamic or functional point of view. Among the lines along which the advance is being made are cell lineage, the life history of cells, the determination of standards of growth, anthropometry and ethnology. The newer useful methods include tissue culture, the x-rays and photomicrography with moving films. The older methods continue to be useful, for the starting point must always be the dissecting room, and many problems can be solved only with the help of experimentation on animals.

From either literary, scientific or historic points of view, the book will give great satisfaction to all interested in any way in the science of anatomy.

PHYSIOLOGICAL PRINCIPLES IN TREATMENT. By W. LANGDON BROWN, M.A., M.D. Cantab., F.R.C.P., Physician to St. Bartholomew's Hospital, with the Collaboration of R. Hilton, M.A., M.B. Cantab., M.R.C.P., Assistant Physician and Assistant Director of the Medical Unit St. Bartholomew's Hospital. Sixth edition. Cloth. Price, $3.75. Pp. 464, with index. New York: William Wood & Company, 1930.

The popularity of this work is attested to by the appearance of this, the sixth, edition, the first edition appearing in 1908, since which time there have been many changes both in theory and in practice. So many notable changes have occurred in the six years following the appearance of the fifth edition, in 1924, that it has been found necessary to submit the whole book to a thorough revision. The author states, "In retrospect I am struck by two facts. One is the much closer association between physiology and medicine now than twenty-one years ago. The other is that a good indication as to the truth of new work can be gathered from the speed with which its effect is found to be spread beyond its original application. Insulin is an outstanding example of this; instances to the contrary need not be pilloried."

Fundamental discoveries in physiology and clinical medicine are correlated in a clear and interesting fashion, and the application of the principles enumerated therein should have a broadening influence on both student and practitioner.

NERVOUS INDIGESTION. By WALTER C. ALVAREZ, M.D., Associate Professor of Medicine, University of Minnesota (the Mayo Foundation). Price, $3.75. Pp. 284. New York: Paul B. Hoeber, Inc., 1930.

This rather small volume is largely an elaboration of two papers previously written by the author: one on the treatment of nervous indigestion, the other on the effects of emotion on the digestive tract. Its theme is functional rather than organic disease, although some attention is given the latter. There is a brief discussion of the physiology of the gastro-intestinal tract.

It is obvious that the author is chiefly concerned with the care of that large group of patients ill with functional disturbances, commonly classified as "neuros," who go in despair from one physician to another, and who frequently, failing to find relief, fall into the hands of charlatans of various kinds. The book is interesting and well written and contains much wisdom and sound advice. It will be read with interest and profit by the older, more mature, practitioners; it should be read by all medical students and recent graduates.

The last chapter of thirty-five pages, entitled "Suggestions for Further Reading," contains well chosen paragraphs from the writings of such men as Sir William Osler, Charles Darwin, Oliver Wendell Holmes and S. Weir Mitchell. These selections serve to emphasize the author's central theme — the skilful treatment of functional ills.

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